AUGUST 1953

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

RULON W. RAWSON

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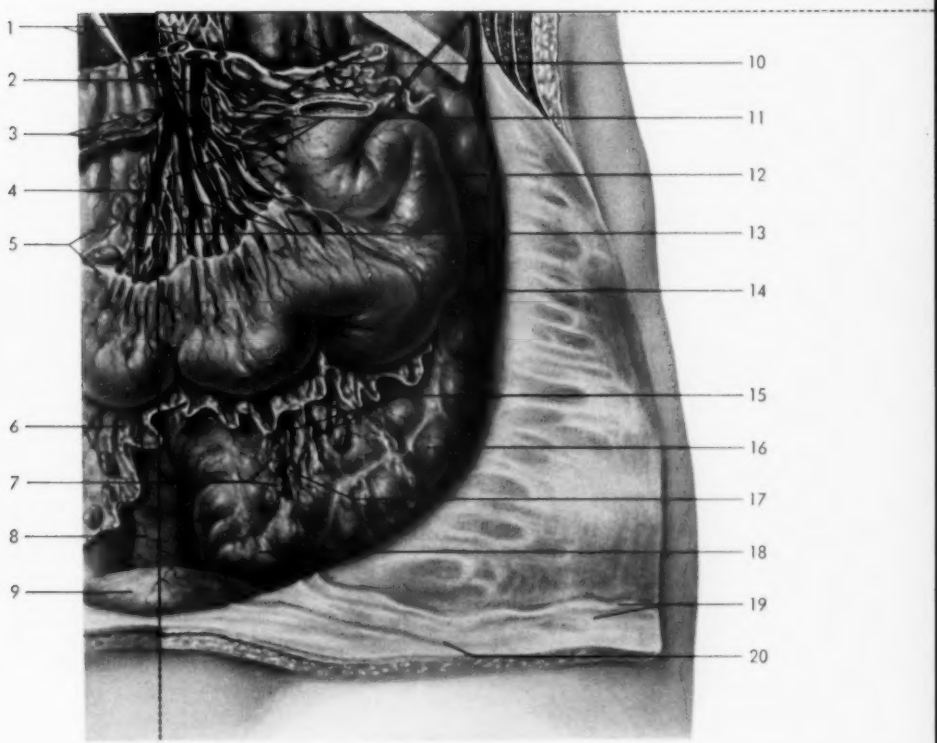

1 Vena cava, aorta and abdominal aortic plexus

2 Branches of superior mesenteric artery and vein

3 Ileocolic lymph node and ileocolic artery and vein

4 Sympathetic abdominal plexus

5 Mesentery

6 Mesenteric lymph nodes

7 Mesocolic lymph nodes

8 Rectum

9 Urinary bladder

10 Inferior mesenteric vein, left colic artery and ureter

11 Intestinal arteries

12 Ileum

13 Intestinal veins

14 Descending colon

15 Branches of sigmoid artery and vein

16 Iliac colon

17 Mesocolon

18 Sigmoid colon

19 Epigastric artery and vein

20 Lateral umbilical ligament

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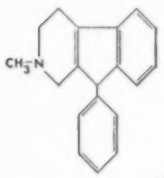

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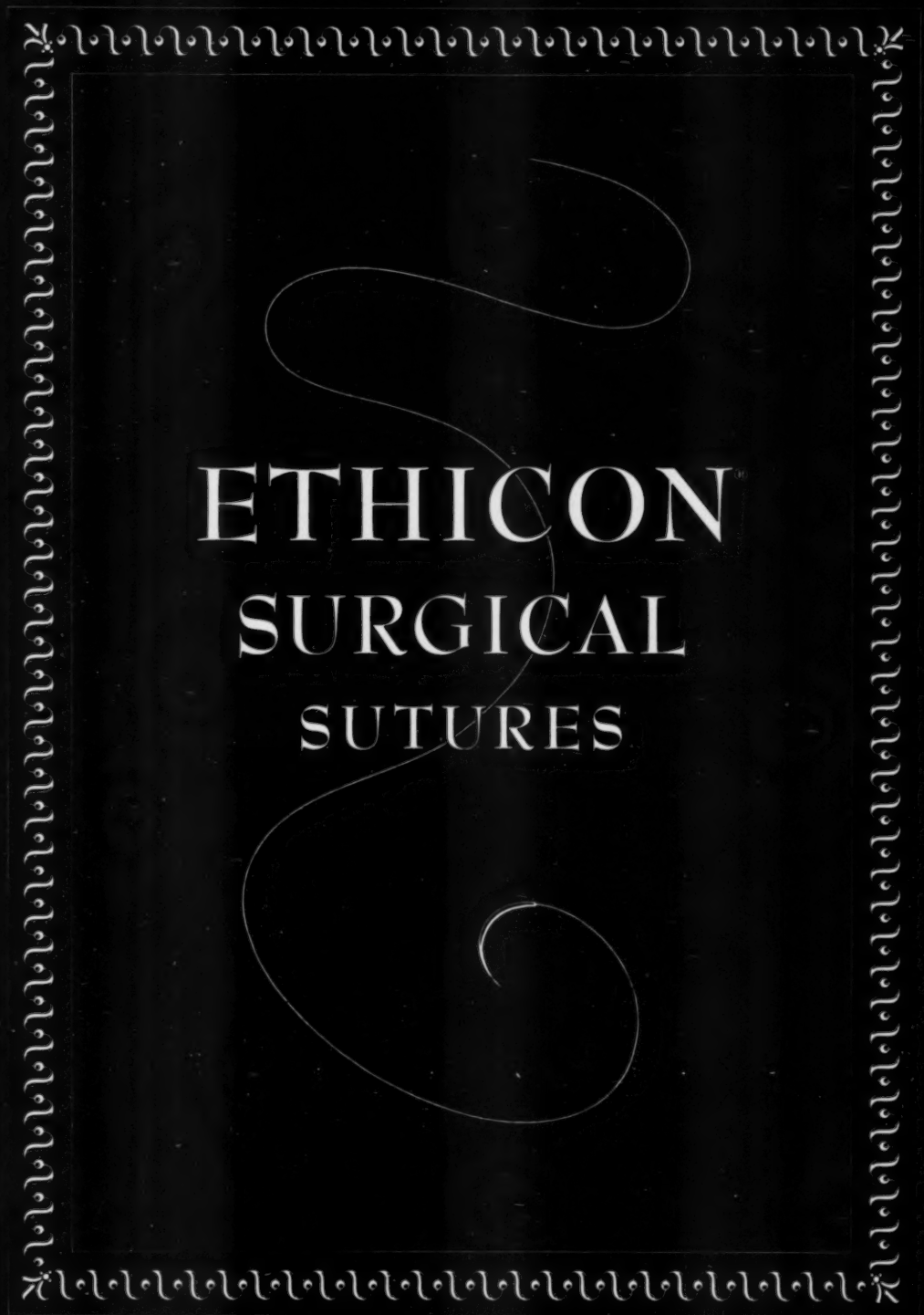
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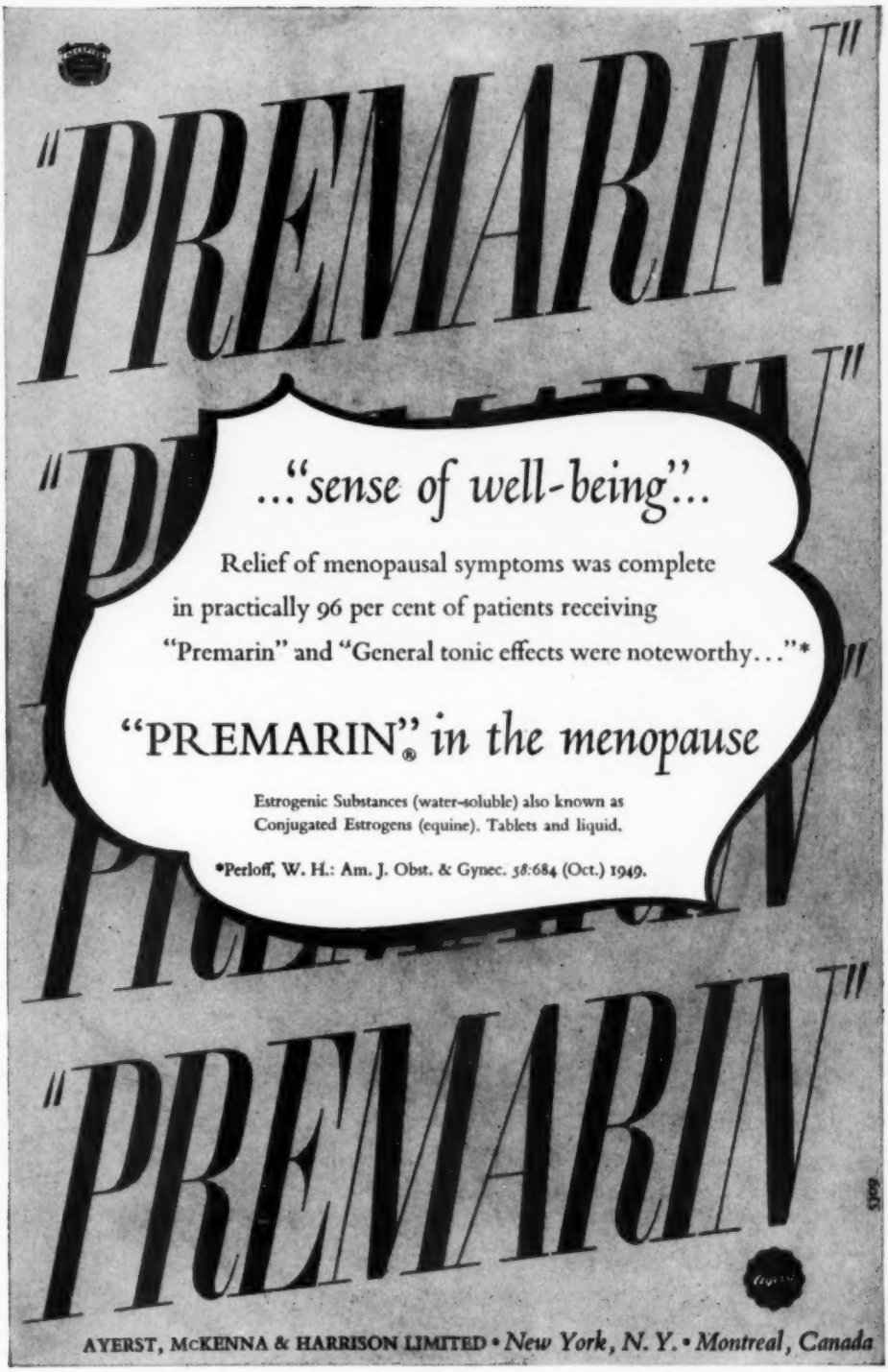
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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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HORMONAL CONTROL OF NEOPLASTIC GROWTH*

RULON W. RAWSON

Professor of Medicine, Sloan-Kettering Division, Cornell University Medical College

When the Fortnight Committee invited me to discuss for you the topic of "Hormonal Control of Neoplastic Growth," I recognized the vastness of the topic, but welcomed the opportunity to discuss this subject because of the newer concepts concerning cancer, which are arising from these studies. As a medical student, I was taught that cancer is an autonomous parasitic growth, which is completely beyond any physiologic controls. As a result of the many studies which are reported in the literature and which are now in progress in many laboratories, I believe that we can now challenge that old concept. Indeed I believe that studies on the relationship of hormones to the development of tumors or to the inhibition of certain metastatic neoplasms make it possible now for us to foster a real hope for eventual control of these diseases by physiologic means.

The medical and biological literature of the last decade and a half is replete with experimental and clinical studies on the relationship of hormones to neoplasms. Such intense activity in this field during the past

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 16, 1952.

fifteen years can be attributed to the availability of potent synthetic and natural hormones and experimental tools and techniques not previously available. To review by brief reference to this vast literature would require much more time than that allotted me. There are, however, excellent reviews on this subject by Loeb,[1] Gardner,[2] Shimkin[3] and Nathanson[4] which I can recommend to you.

Before discussing some of the modern studies, it should be pointed out that in 1889 Schinzinger,[5] a German surgeon, advocated oophorectomy in premenopausal women with cancer of the breast because of the atrophy of the breast which follows loss of ovarian function. Several years later in 1896 Beatson,[6] a surgeon from Glasgow, reported striking beneficial changes in two premenopausal women with extensive and metastatic cancer of the breast whom he had oophorectomized and treated with thyroid.

Hormonal Factors in the Production of Tumors in Experimental Animals

The first carefully planned and executed study of the glands of internal secretion and their relationship to cancer was that reported in 1919 by Dr. Leo Loeb.[7] He demonstrated in mice having a high incidence of breast cancer that ovariectomy of the young prevented the development of mammary cancer. Castration after the age of six months had practically no effect on the development of these tumors.

In 1932, Lacassagne[8] first succeeded in producing carcinoma of the mammary gland in male mice belonging to high tumor strains by injecting large amounts of estrogenic hormones over long periods of time. Negative results were obtained when estrogens were administered to male mice belonging to strains in which spontaneous mammary tumors in the females are uncommon. These experiments were confirmed very promptly by Burrows,[9] and Gardner, Smith, Allen and Strong.[10]

Since that time there have been many reports of tumors produced in animals after prolonged treatment with various estrogenic compounds both steroidal and non-steroidal.

Lacassagne[11] has demonstrated that the influence of various estrogens on the formation of breast tumors in mice appears to be proportional to their estrogenic activity. Gardner[12] has reported that the administration of estrogens to hybrid mice from matings of high tumor strains and low tumor strains resulted in a high incidence of tumors in mice

whose mothers were of the high tumor strain but not in those whose mothers were of a low tumor strain.

Gardner, Allen, Smith and Strong[13] reported in 1938 the appearance of a metastasizing transplantable cancer of the cervix in a mouse of a high tumor strain following the injection of estrogens for ten months. Subsequently, Allen and Gardner[14] have produced several cancers of the cervix in two groups of hybrid mice.

Lipschütz, Rodriguez and Vargas[15] have reported that the administration of estradiol monobenzoate to guinea pigs resulted in the development of uterine and extrauterine fibroids and endometrial polyps which extended into the vagina. They[16] have reported subsequently that the simultaneous administration of testosterone or progesterone with the estrogen prevented the development of such uterine fibroids.

Gardner, Dougherty and Williams[17] studied the lymphoid tissues of seven strains of mice receiving estrogens over a long period of time. In three strains (C_3H, CBA, P.M.) they observed 15 per cent incidence of lymphosarcomas, in the other strains (C_{121}, JK, A and C_{57}) they observed an incidence of 2 to 5 per cent. It is of interest that the simultaneous administration of testosterone with estrogens in one of the more susceptible strains resulted in an apparent inhibition to the development of such lymphoid tumors.

Hooker and Pfeiffer[18] have reported that the administration of estradiol benzoate or of stilbestrol to male mice of the A strain resulted in the development of interstitial cell tumors of the testes which apparently were capable of producing androgens. They postulated that the mechanism of this tumor's genesis was through a stimulatory effect on the pituitary's production of luteinizing hormone, which in turn acted to stimulate growth of the Leydig cells.

Woolley and his associates[19-21] have followed male and female mice of several strains, which were castrated between one and six months of age. In these animals they have observed hyperplasia and neoplastic changes in the adrenal cortices. Some of these tumors were observed to exert androgenic effects on the hosts and others exerted estrogenic effects. In several of their mice tumors of the mammary glands and of the pituitaries were observed after the development of the adrenal tumors. At present, we have a patient on the research ward of the James Ewing Hospital, who presents a similar situation. This female patient has had both breasts removed for malignant tumors. She now

has the picture of a functioning tumor of the adrenal cortex. We might speculate as to the possibility of the adrenal tumor having hormonal effects on the breasts which resulted in tumors.

Leo Loeb was the first investigator who explored the role of the pituitary in the development of mouse tumors. In 1939, Loeb and Kirtz[22] reported that they had successfully transplanted pituitaries of inbred mice to their siblings. Such transplants caused marked development and secretory activity in the mammary glands. They caused a marked increase in the incidence of mammary cancer in females of the A strain over that observed in virgin mice without transplants. In a small number of mice with transplants of the anterior pituitary, precancerous changes were observed in the vaginal cervical tract.

In 1941 Evans and his associates[23] reported that the administration of pituitary extracts rich in gonadotropic hormones caused placentomas in normal but not in hypophysectomized rats. A pituitary preparation rich in lactogenic hormone favored the production of such tumors in normal, adrenalectomized or hypophysectomized rats, but not in ovariectomized animals.

More recently, in a series of important studies, Moon and associates[24-26] have reported that the prolonged administration of growth hormone to intact rats of the Long Evans strain resulted in the development of lymphosarcomas of the lung and of the peribronchial lymph nodes, in solid tumors of the ovaries and in atypical hyperplasia of the ovarian follicles which resembled granulosa or interstitial cell tumors of the ovary. Fibroadenomata of the breast occurred more often and were larger than in the untreated controls. In the adrenals of these animals the adrenal cortices showed nodular changes and the medullae were hypertrophic and proliferative with areas of neoplastic cells invading and displacing the adrenal cortices. In three rats the neoplastic medullary tissue grew through the cortex and was macroscopically visible on the surface of the adrenal gland.

The pituitaries of these animals were found to contain smaller, less granular and fewer acidophils than those of the controls, while the basophils were increased in number and resembled those observed in castrate rats. In one rat, the pituitary contained numerous small basophilic adenomata.[27]

It is of interest that the administration of growth hormone to hypophysectomized rats of the same strain resulted in a normal growth

response but failed to produce any neoplastic changes.[28] This obviously suggests that some other pituitary hormone or a hormone of the target gland of some other pituitary hormone is necessary to the development of such tumors. More recently these same investigators[29] have reported that the development of cancers in response to treatment with methylcholanthrene is markedly diminished in hypophysectomized rats.

During the past decade, we have had a variety of goitrogenic agents made available. These agents are goitrogenic by virtue of two actions, i.e., secondary to a hypothyroidism, which they produce, they cause an increased secretion of TSH by the pituitary, and they enhance the action of TSH. With these agents at hand, several investigators have administered them to rats or mice over long periods of time. In 1944, Bielschowsky[30,31] reported that the administration of 2-acetylamino-fluorine and allyl thiourea to rats resulted in the production of thyroid tumors, both benign and malignant. Shortly afterwards, Griesbach, Kennedy and Purves[32] reported that the administration of a rape seed diet resulted in the development of hyperplastic goiters which later manifest tumors of the thyroid. More recently, these same investigators[33] have produced a highly malignant cancer of the thyroid by administering methyl thiouracil to their rats.

Dalton, Morris and Dubnik[34,35] have reported that the administration of thiouracil to mice of a high tumor strain resulted in the development of metastasizing and transplantable cancers of the thyroid, whereas the same agent when administered to mice of a low tumor strain, produced hyperplasia and benign tumors of the thyroid. Money and Rawson[36-38] have observed that the administration of thiouracil to rats of the Sprague-Dawley strain resulted in a variety of benign adenomas. When they combined thiouracil with subcutaneous injections of dibenzanthracene, they were able to produce a transplantable cancer of the thyroid. It is concluded that such cancers are dependent on the growth stimulus of the pituitary thyroid stimulating hormone and upon an inherited cancer susceptibility or the action of a carcinogen.

Observations Suggesting Possible Hormonal Factors in Genesis of Human Cancer

It would be premature to conclude from the above experimental observations that these various hormones are a cause of cancer as seen in man. However, it would be quite unsound to discard them as of no

consequence in human studies. Indeed there are several clinicopathologic states, recently described by thoughtful and observing students which give credence to the theory that similar situations might apply in man.

In 1922, Schröder of Rostock[39] reported a forty-five year old patient in whom he had found a large granulosa cell tumor of the ovary, which was associated with endometrial hyperplasia and an early carcinoma of the endometrium. Dockerty[40] and Hodgson, Dockerty and Mussey[41] have reported a variety of pathologic lesions which co-existed with granulosa cell tumors in sixty-two patients seen at the Mayo Clinic. Thirty-two (51.6 per cent) of these feminizing tumors were associated with uterine fibromyomata, eight (or 12.9 per cent) with carcinoma of the uterine fundus and three (or 4.8 per cent) with carcinoma of the breast. Banner and Dockerty[42] have reported that in twenty-three patients with theca cell tumors myohypertrophy and/or fibromyomas were found in thirteen, endometrial adenocarcinoma in three, adenocathanthoma of the cervix with metastases in one and epidermoid carcinoma of the cervix in one. More recently Dockerty and Mussey[43] have reported that the incidence of endometrial cancer in a series of eighty-seven patients with granulosa cell or theca cell tumors was more than 15 per cent. In three of their patients endometrial and breast carcinomas were found to exist or to occur shortly after the ovarian tumors had been removed. Smith[44] has stated that 1/5 of his patients with granulosa cell tumors also had endometrial cancers. Smith[45] has also noted a cortical stromal hyperplasia in the ovaries of 80 per cent of his postmenopausal patients with endometrial cancer. This cortical stromal hyperplasia has been described as an increased thickness and cellular density in the cortical stroma with numerous whorls and interlacing fascicles weaving about variable numbers of capillaries and dipping irregularly into the relatively cellular eosinophilic medullary stroma. Enlarged nuclei with abundant coarse granular chromatin have been described in these cortical stromal cells. Because these structures take fat stains it has been suggested that they represent estrogen secreting tissue. In subsequent studies by Woll, Hertig, Smith and Johnson[46] the incidence of cortical stromal hyperplasia in patients with endometrial cancer was found to vary in various decades between 56 and 92 per cent whereas for a control age group it was found to vary between 36 and 43 per cent. These investigators also reported that thecomas in patients with endometrial cancer are 9 times

as common as in a control group.

Sommers and Teloh[47] have reported that cortical stromal hyperplasia was observed in 83 per cent of 100 autopsied patients with cancer of the breast as opposed to an incidence of 37.5 per cent in a control group. In a subsequent report McManus and Sommers[48] suggested that the therapeutic effects of castration for metastatic cancer of the breast in patients shown to have cortical stromal hyperplasia are better than they are in patients whose ovaries do not show cortical stromal hyperplasia.

Data from the Canton of Zurich, Switzerland,[49] where the death rate from thyroid cancer has decreased subsequent to the use of iodized salt, would suggest a similar relationship between thyroid neoplasia and goitrogenesis, presumably mediated via the pituitary in the human, as has been demonstrated in rats. In this canton, iodized salt was first introduced in 1923. Its use had gradually increased to 90 per cent by 1950. The incidence data for deaths from cancer of the thyroid per 100,000 for males and females were as follows: 1906-1915, 2.04 and 1.43; 1916-1925, 2.12 and 1.59; 1926-1935, 1.40 and 1.74; 1936-1945, 0.65 and 0.94. This marked decrease in cancer of the thyroid strongly suggests that prophylaxis of goiter is a prophylaxis against cancer of the thyroid. Presuming that goitrogenesis in humans is mediated as in rats by the patient's increased production of TSH, we might suggest that TSH contributes to the genesis and growth of thyroid cancer.

Unfortunately, our techniques for demonstrating gonadal or pituitary hormones in blood or urine are still quite inadequate and we are unable to report on the metabolism of ovarian or pituitary hormones. However, the late Dr. Konrad Dobriner of the Sloan-Kettering Institute and Dr. Seymour Lieberman now of the College of Physicians and Surgeons have reported[50, 51] extensive studies on the urines of normal humans and patients with various neoplastic diseases. In these studies, they have concentrated on a separation of the various steroids in the urine. The major steroids isolated by them from the urines of normal men and women were androsterone, etiocholanolone, 11-hydroxy-androsterone and 11-keto-etiocholanolone. In the urine of patients having a variety of cancers, they demonstrated another steroid which they very seldom found in normal humans, 11-hydroxy-etiocholanolone. This steroid, because of its structure, is thought to be a metabolite of one of the adrenal steroids, normal or abnormal.

Experimentally Induced Hormonal Control of Human Cancer

A third approach to this problem is found in the clinical experiments in which attempts have been made to affect the course of certain human cancers by altering the hormonal environment.

The sequence of events, which led to the endocrinologic studies in patients with metastatic carcinomas of the prostate is one of the most fascinating accounts in experimental medicine. In 1936, the Gutmans of the College of Physicians and Surgeons[52] reported that they had found a high titer of phosphatase in the metastases of a patient who had carcinoma of the prostate, which reacted only at an acid pH level. Subsequent studies by the Gutmans[53] and by Woodard[54] demonstrated an elevated acid phosphatase level in the blood of patients with metastatic cancer of the prostate. The Gutmans[55] then demonstrated that this enzyme is present in normal prostates, and that it could be increased in the prostates of monkeys by administering testosterone.[56]

Studies done by Huggins and associates[57, 58] at about the same time. demonstrated that prostatic secretion in dogs was decreased by castration. They also demonstrated that the administration of testosterone caused a regeneration of the prostate and that this could be inhibited by the administration of estrogens.

Huggins, Hodges and Stevens[59, 60] then applied these physiologic considerations in the treatment of patients with metastatic cancer of the prostate. They castrated twenty such patients and observed an appreciable clinical improvement in fifteen patients. There was a fall in the serum acid phosphatase in all but two cases. There was an increase in body weight and an increase in the hemoglobin levels. Shrinkage of the primary lesions was also observed. They also reported that the administration of testosterone to such patients resulted in an increase in the serum acid phosphatase whereas the administration of estrogenic hormones caused a fall in the blood levels of this enzyme.

These observations by Huggins have been widely confirmed during the past decade. An analysis of pooled cases, from fourteen clinics, which had received endocrine treatment, has recently been published by Nesbit and Baum.[61] Of 115 patients with and without metastases on admission treated with diethylstilbestrol only 18.3 per cent survived five years. Twenty-six per cent of 359 cases treated by castration, and 36.3 per cent of 113 patients treated by castration and with diethylstil-

bestrol survived five years. Only 9 per cent of 504 untreated cases followed between 1925 and 1940 survived for five years.

In 1945 Huggins and Scott,[62] who reasoned that relapses in patients who had made favorable responses following castration were due to androgens being elaborated by the adrenal, did bilateral adrenalectomies in four previously castrated patients who had later relapsed. Three of these patients died of adrenal insufficiency in the postoperative period. In one patient who survived for more than three months they reported that there was relief of pain and even shrinkage of the primary tumor. The fact that cortisone has recently been available in fairly adequate amounts has made it possible to expand studies on the effect of adrenalectomy in cancer of the prostate and other diseases. In 1952 Huggins and Bergenstal[63] reported their observations on seven patients with metastatic cancer of the prostate whose disease had relapsed following previous responses to anti-androgenic therapy. One patient died postoperatively. In four patients some of the following effects were observed: relief of intractable bone pain, gain in body weight, and a reduction in acid phosphatase. In two patients there was a significant shrinkage of large nodular prostates. In two patients no improvement whatsoever was observed.

West, Hollander, Whitmore, Randall, and Pearson[64] have studied the effect of adrenalectomy in eleven patients with advanced carcinoma of the prostate who had relapsed after previous response to castration and estrogen therapy. Transient relief of pain was observed in ten of their patients. Shrinkage of tumor tissue was observed in two of their patients. Unfortunately, objective improvement was not observed in any more of their cases.

Notwithstanding the theory originally advanced by Huggins that the benefit of castration and now of adrenalectomy in these patients is due to removal of the body's two major sources of testosterone and other androgens, it has been demonstrated by Brendler, Chase and Scott[65] and by Hollander and Whitmore[66] that the administration of testosterone is followed by exacerbation of the disease in only a fraction of the cases. Hollander and Whitmore[66] have observed in twenty-two patients with metastatic prostatic cancer that testosterone caused a rise in acid phosphatase in only nine cases and an increase in symptoms in only five cases. It would appear then that we may have to look for some other mechanism with which to explain these well-estab-

lished therapeutic effects of castration in prostatic cancer.

It was stated earlier that Schinzinger,[5] a German surgeon was the first to suggest castration for cancer of the breast. Beatson[6] a surgeon from Glasgow, reported in 1896 having castrated two young women with advanced metastatic cancer of the breast. He reported relief of pain and regression of the cancerous growths in these patients. Following Beatson's report, there were numerous reports of this type of treatment for mammary cancer. Then for nearly twenty-five years, there was no activity in this field. Between 1921 and 1930 several writers recommended roentgen castration of premenopausal women with cancer of the breast. In 1938, Dresser[67] reported on a series of fifty-seven patients, whose ovaries he had attempted to destroy with x-ray. He reported beneficial effects in thirty per cent of his cases. In 1945, Adair, Treves, Farrow and Scharnagel[68] reported observations on 335 women with advanced carcinoma of the breast, whom they had castrated, 304 by x-ray and thirty-one surgically. In this group they observed objective benefit in only 15 per cent. They concluded that castration in general exerts only a temporary beneficial effect. In cases which are improved, the growth process appears to be retarded for about two years. They also reported that castration in eight males with advanced carcinoma of the breast resulted in spectacular regressions of the disease. In 1948, Treves[69] reported the results of castration in thirteen male patients with advanced carcinoma of the breast. The results in this group were just as spectacular as in the previous series with regression of local lesions and healing of skeletal metastases.

In 1939, Nathanson[70] reported that prolonged administration of testosterone to female mice of a high mammary cancer strain resulted in a significant decrease in the number of mammary tumors which ultimately developed. Following this report, there appeared reports by Farrow and Woodard[71] and by Fels[72] on the treatment of metastatic cancer of the breast with testosterone. The former workers reported symptomatic improvement without objective evidence of benefit. The latter investigator reported improvement in one patient with regression in soft tissue and bony metastases. Notwithstanding the unspectacular results in some of the earlier reports, continued studies have resulted in greater understanding and significant therapeutic results in patients with metastatic cancer of the breast treated with testosterone.

In 1944, Haddow and associates[73] first described the use of synthetic

estrogens in the treatment of carcinoma of the breast and of other sites. In this country, Nathanson[74] was the first to demonstrate a therapeutic effect of estrogens in postmenopausal women with advanced mammary carcinoma. During the past eight years, several clinics have been actually studying the therapeutic effects of androgenic and estrogenic hormones on human mammary cancer.

The policy has been to administer testosterone propionate intramuscularly in doses of 50 to 100 mg. three times a week to menstruating or early postmenopausal patients. Estrogens are administered orally as ethinyl estradiol 1 mg. three times daily, or diethylstilbestrol 5 mg. three times daily to women who are ten or more years postmenopausal.

The results of such therapeutic programs in the breast clinic of Memorial Center[75] are as follows: In the testosterone treated patients: recalcification of osteolytic lesions has been observed in 19 per cent of 133 patients having osseous metastases. In 174 patients, with soft tissue disease, improvement, i.e., significant and measurable decrease in the size of palpable lesions and healing of ulcers has been observed in 22 per cent. A decrease in the size of pulmonary nodules has been observed in only two of forty-eight cases. In the estrogen series, twenty-eight per cent of thirty-six patients with osseous disease have shown recalcification of one or more lesions, 41 per cent of 111 patients had significant improvement in the soft tissue sites of disease, and 33 per cent of thirty-nine patients with pulmonary disease have shown shrinkage of the pulmonary metastatic nodules. Although there is considerable variability in the rate of response, most successfully treated cases demonstrate improvement within three months.

A study now in progress by members of the Breast Clinic and the Radiotherapy Service at Memorial Center suggests that the combination of x-ray therapy with hormonal treatment is more effective in promoting healing of osseous and soft tissue lesions than is either x-ray or hormonal treatment alone.

Therapy with testosterone often leads to troublesome virilization, hirsutism, deepening of the voice, acne, increased libido and clitoral hypertrophy. It may also be complicated by sodium and water retention necessitating diuretic measures.

Recently Huggins and Yuan Dao[76] have reported their observations in eight patients who had been adrenalectomized for advanced mammary cancer. There was one postoperative death. One male patient with

metastatic carcinoma of the breast who had failed to respond to castration done six months prior to the adrenalectomy showed a satisfactory regression of disease. There was no amelioration of the breast disease in three women with the disease. In three women with metastatic cancer of the breast there was significant shrinkage of the tumors following adrenalectomy. Unfortunately two premenopausal patients who showed favorable responses following adrenalectomy were oophorectomized at the time of adrenalectomy and thus cannot honestly be included in any evaluation of adrenalectomy as a therapeutic measure for this disease.

West et al.[64] have studied the effect of adrenalectomy in nine patients with advanced carcinoma of the breast, who had previously been treated by castration and steroids but had either failed to respond to such treatment or had relapsed following initial responses. Objective evidence of improvement was observed in three cases. There was shrinkage of soft tissue disease and evidence of improvement in skeletal lesions. The improvement, though striking, was only transient. However, it has been great enough to warrant further investigation for at least a better understanding of the mechanism involved in those patients who do respond to this procedure.

It might seem to be paradoxical, but beneficial effects have also been obtained from the administration of cortisone or of ACTH in patients with certain types of tumors. It was first demonstrated by Murphy and Sturm[77] and then by Heilman and Kendall[78] that the administration of Kendall's Compound E (now known as cortisone) to mice bearing lymphosarcomas resulted in a shrinkage of the tumors. Pearson and associates[79] reported in 1949 that the administration of cortisone or of ACTH to patients with certain lymphomatous diseases resulted in a spectacular shrinkage of the tumor masses with metabolic changes which reflected the rate and amount of tumor destruction. Cessation of hormonal administration is followed by prompt recurrence of the tumors. Subsequent studies have revealed that some patients with lymphosarcoma, chronic lymphatic leukemia, or multiple myeloma can be successfully treated repeatedly with either of these hormones or with 11-hydroxy-cortisone (Compound F). It has also been demonstrated that patients with these diseases can be carried on cortisone for prolonged periods of time and that the disease is held under control by such treatment if dosage of the hormone is adequate.[80]

The same investigative group has also explored the therapeutic

effects of these hormones in acute leukemia and other neoplasms.[79, 81] They observed that acute leukemia responds once or twice to such an altered hormonal environment. Other tumors have not been favorably affected by this form of treatment.

Recent studies have also demonstrated that many cancers of the thyroid can very effectively be brought under the control of certain physiologic mechanisms. Indeed a large percentage of metastatic tumors of the thyroid has been forced to function much as normal thyroid tissue does. Although it has been demonstrated[82] that in 100 cancers of the thyroid forty-six possessed the capacity to concentrate radioactive iodine, none of these tumors was capable of concentrating any more than a fraction of the iodine trapped by normal thyroid tissue. However, in one half of a group of forty-five patients with metastatic cancer of the thyroid, it has been demonstrated[83] that ablation of the normal thyroid results in previously non-functioning metastatic lesions assuming the function of normal thyroid tissue, i.e., concentrating radioactive iodine, and even maintaining the patient in a euthyroid state. It has also been demonstrated that the administration of thyrotropic hormone will induce function in the tumors of about one-third of the cases studied. Finally, it has been demonstrated in 70 per cent of a series of thirty-six previously totally thyroidectomized patients having skeletal or pulmonary metastases that the prolonged administration of thiouracil or of tapazol, agents which augment the action of thyrotropic hormone, results in the metastatic lesions acquiring maximum capacity to concentrate radioactive iodine. From the practical point of view, this has permitted us to administer radioactive iodine in therapeutic amounts which have had a demonstrable cancericidal effect.

Although none of the endocrine treatments of cancer discussed have been demonstrated to have lasting curative effects, I believe that these considerations on the hormonal influences on cancer can be considered as major and important steps towards ultimate understanding and rational treatment of these diseases.

Summary

It has been demonstrated that the administration of estrogenic hormones to experimental animals results in the production of tumors of the following tissues: breast, cervix, uterus, testes and lymph nodes. It has been demonstrated that the administration of pituitary hormones or the

induction of increased elaboration of certain pituitary hormones results in the development of uterine placentomas, ovarian, lymphatic, lung, adrenal, breast, testicular and thyroid tumors.

It has also been demonstrated that by altering the hormonal environment, the following human tumors can be made to recede or to function like normal tissues, prostate, breast (male and female), lymphatic and thyroid. These observations are being further investigated for clues which may ultimately lead to physiologic methods of controlling the development and course of such tumors.

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PARATHYROID HORMONE AND MINERAL METABOLISM*

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BOTH in hypoparathyroidism and in hyperparathyroidism marked changes appear in the calcium and phosphorus levels of the serum and in the excretion of calcium and phosphorus in the urine. These changes indicate that parathyroid hormone must have a considerable influence upon the metabolism of these two substances. This relationship is further emphasized by the fact that the changes found in hyperparathyroidism are essentially the reverse of the changes found in hypoparathyroidism. In hyperparathyroidism there is an increase of the calcium content of serum and urine and of the phosphorus content of the urine. The phosphorus content of the serum is, however, decreased. In hypoparathyroidism the calcium content of the serum is low, the phosphorus content of the serum high and both calcium and phosphorus are practically absent from the urine.

It is well known that extensive bone lesions are found in many cases of hyperparathyroidism. These skeletal changes are evidently caused by rapid decalcification leading to osteitis fibrosa.[1] Osteitis fibrosa does not represent a specific skeletal disease, but is a non-specific reaction secondary to rapid demineralization. In hyperparathyroidism not only is fibrous osteitis present but in addition cysts and brown giant-cell tumors, so-called osteoclastomas, are frequently found. After removal of the parathyroid adenoma, the changes of the calcium and phosphorus metabolism return to normal, the bone pain disappears, and in many cases extensive recalcification of the skeleton takes place. Sometimes even sclerosis of the formerly decalcified skeleton results.

CAUSATION OF BONE LESIONS IN HYPERPARATHYROIDISM

The mechanism by which excessive excretion of parathyroid hormone leads to these bone lesions must be a complicated one. Jaffe and

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his associates[2] were the first to demonstrate that injection of parathyroid hormone in young guinea pigs causes bone changes which in many respects resemble the osteitis fibrosa of patients with hyperparathyroidism. The rapidly growing bones and areas of rapid growth in the same bone are most susceptible to the influence of parathyroid hormone. These results have been generally confirmed. Jaffe,[3] just like Thomson and Collip[4] and also Selye,[5] assumed that parathyroid hormone stimulates proliferation of the osteoclasts of the bone marrow with an ensuing increased erosion of bone trabecules, followed by rapid decalcification and osteitis fibrosa. The changes in calcium and phosphorus metabolism according to this explanation should then be considered the result of excessive activity of the osteoclasts of bone.

The frequent occurrence of osteoclastomas in hyperparathyroidism seems to favor the assumption that parathyroid hormone produces a primary proliferation of osteoclasts. In this connection it is important to emphasize that rather frequently the appearance of a giant-cell tumor represents the first sign of hyperparathyroidism. Even when the roentgen examination of the rest of the skeleton is apparently normal, the development of such an osteoclastoma must always raise the suspicion of hyperparathyroidism. Giant-cell tumors, particularly of the skull, are often the first indication that an adenoma of one or more parathyroids should be sought.[6] In the course of the years we have observed this in at least three patients. In these three cases the osteoclastomas were situated in the frontal bone, the maxilla and the mandible respectively. In one of these cases signs of generalized skeletal decalcification became apparent four years after a resection of the mandible had been performed. Only then were hypercalciuria, hypercalcemia and hypophosphatemia found. In this case, too, the diagnosis of parathyroid adenoma was finally confirmed at operation. If at the time of the mandibular resection the possibility of hyperparathyroidism had been seriously considered, the latter operation might well have been avoided; after removal of a parathyroid adenoma such giant-cell tumors are usually absorbed and ultimately recalcify. The occasional development of giant-cell tumors in the early stages of hyperparathyroidism is a point in favor of the theory that hypersecretion of parathyroid hormone leads directly to a proliferation of osteoclasts. Such osteoclastoma formation is never observed in other diseases with rapid decalcification, hypercalcemia, and hypercalciuria, as for instance in multiple myeloma or in rapidly spread-

ing metastatic disease of the skeleton.

Albright has emphasized important points which at the time seemed to militate against the conception that the bone lesions in hyperparathyroidism are caused by hyperactivity of osteoclasts. He agreed, of course, that during the destruction of bone by osteoclastic erosion the liberation of large quantities of calcium phosphate could easily explain why hypercalcemia, hypercalciuria, and hyperphosphaturia are constant signs in hyperparathyroidism. However, since calcium phosphate is freed in the process of resorption of bone, it is at first view difficult to understand why overproduction of parathyroid hormone should lead at the same time to an increase of serum calcium but to a decrease of serum phosphate. In order to find an explanation of this mysterious hypophosphatemia, Albright and his associates extensively studied the phosphorus metabolism in hypo- and hyperparathyroidism.

It had been known for many decades that following parathyroidectomy in dogs the phosphorus excretion in the urine may be markedly reduced In Greenwald's experiments the urinary output of phosphorus was as low as 2 per cent of the preoperative values.[7] At the same time the serum phosphate increased markedly. In 1944 and 1947 Tweedy and associates[8, 9] confirmed these findings by using radioactive phosphorus. They observed that within twenty-four hours after thyroparathyroidectomy in rats, treated previously with radioactive phosphorus, the urinary and fecal excretion of radiophosphorus decreased significantly. A reversal of the decreased urinary excretion of radioactive phosphorus could be obtained during the first twenty-four hours postoperatively by the injection of 500 units of parathyroid hormone. The difference between such short term experiments on animals and chronic conditions as encountered in clinical medicine is clearly elucidated by the following observation. As early as forty-eight hours after the operation, the urinary and fecal excretion of radiophosphorus of the thyroparathyroidectomized rats began to increase and fifteen to twenty-six days later the quantities excreted even exceeded the preoperative values. On the other hand, after inadvertent removal of all parathyroids in humans, the calcium and phosphorus excretion remain low for many years.

In 1929, Albright and Ellsworth[10] reported that in normal human subjects and in patients with hypoparathyroidism injection of parathyroid hormone is followed by a considerable increase of the amount of

phosphate excreted in the urine. This, of course, is consistent with the decreased urinary excretion of phosphates observed after removal of the parathyroids. Albright and his associates emphasized the possibility that this hypophosphaturia induced by parathyroid hormone was the causative mechanism leading to the changes of the calcium and phosphorus metabolism observed in hyperparathyroidism.[10] The proliferation and hyperfunction of the osteoclasts of the bone marrow with ensuing decalcification should then be considered secondary phenomena. Albright reasoned that due to this hyperphosphaturia, the inorganic phosphorus of the blood serum decreased. The formula $\frac{Ca \times P}{pH} = K$ (constant) indicates that the undersaturation of the phosphates in the blood will require an increase in the calcium content of the circulating plasma. This rise of the serum calcium must be followed by hypercalciuria. This excess calcium can be obtained either from food or from the skeleton. If the calcium intake from the gastrointestinal tract is not sufficient to meet the increased requirement of calcium, then resorption of calcium and phosphorus from the skeleton becomes necessary. The ensuing skeletal decalcification follows a rapid course which leads to generalized osteitis fibrosa. In this way Albright considered the bone lesions in hyperparathyroidism to be the result of a chain of biochemical changes starting with an excess of phosphates excreted in the urine under influence of parathyroid hormone. Albright's experiments not only emphasized the role of the kidney in the pathogenesis of the biochemical syndrome as seen in hypo- and hyperparathyroidism, but at the same time minimized the direct influence of parathyroid hormone on the osteoclasts of the bone marrow.

Now, after years of discussion, Albright[11] has modified his original hypothesis. He, too, agrees that, irrespective of its influence on kidney function, the parathyroid hormone also exerts a direct influence on calcium and phosphorus metabolism. This follows from the following experimental results. When both kidneys and parathyroids are simultaneously removed, the serum calcium decreases in the same way as when the parathyroids alone are extirpated. Monahan and Freeman[12] reported that the injection of parathyroid hormone in dogs which have undergone a bilateral nephrectomy causes hypercalcemia. When parathyroid hormone is administered to dogs in whom both kidneys and parathyroids have been removed, hypercalcemia also results.[13] Collip and associates[14]

in 1934 and McJunkin and associates[15] in 1937 observed that injection of parathyroid hormone leads to bone lesions not only in normal rats but also in nephrectomized rats. Finally, Albright and his associates[16] also produced the characteristic bone lesions of hyperparathyroidism by the administration of parathormone to nephrectomized rats. All these experiments seem to prove beyond doubt that parathyroid hormone causes changes of calcium metabolism and of bone, even after the removal of both kidneys. The disturbance of calcium and phosphorus metabolism in hyperparathyroidism therefore develops independent of renal mechanisms in general and of renal hyperexcretion of phosphate in particular. The direct influence of parathyroid hormone on bone was clearly demonstrated by the elegant experiments of Barnicot[17] who transplanted parathyroids attached to a piece of bone intracerebrally and thereby produced lesions in the bone contiguous to the parathyroid transplants. Thus, the older investigators were evidently correct in assuming that parathyroid hormone directly increases osteoclastic erosion of bone and hereby causes generalized osteitis fibrosa. All this also sheds light upon the experiences of McLean and Bloom[18] who at microscopic examination found an accumulation of bone salts in the lumen of the venules of the cancellous bone of rats treated with parathyroid hormone. These bone salts, which were also seen in the macrophages, must derive from erosion of bone trabeculae under the influence of parathyroid hormone.

Causation of Hypophosphatemia in Hyperparathyroidism

Even if it is now the general consensus that the excess of parathyroid hormone excreted in hyperparathyroidism causes excessive osteoclastic absorption of cancellous bone, the hyperphosphaturia under influence of parathyroid hormone, so clearly demonstrated by Albright and his colleagues, remains an important factor for the correct understanding of the pathologic physiology of hyperparathyroidism. As mentioned above, rapid destruction of cancellous bone under influence of the hyperfunction of the osteoclasts, stimulated by excessive production of parathyroid hormone, should give rise to the liberation of calcium phosphate, leading to an increase not only of serum calcium but also of serum phosphate. The actual decrease of the inorganic phosphate content of the serum in hyperparathyroidism must then be connected with the

increase of the excretion of phosphates in the urine soon after injection of parathyroid hormone.

It should be remembered that the total quantity of phosphates, present in 5 liters of circulating blood, does not exceed 200 mg. in total. An increase of the phosphate excretion in the urine could well influence the relatively small phosphate content of the serum. Parathyroid hormone increases renal excretion of phosphate at the same time that it mobilizes calcium phosphate from the bones. The excessive quantities of phosphate excreted in the urine under influence of the parathyroid hormone are so large that notwithstanding the increased calcium phosphate transport to the blood, the serum phosphate decreases. It will be brought out later that no such influence of parathyroid hormone on the renal excretion of calcium has been demonstrated.

In this way the observations of Albright and his associates have explained the hypophosphatemia which occurs in hyperparathyroidism in sharp contrast to the hypercalcemia. This important fact remains, even though Albright's theory that the skeletal decalcification in hyperparathyroidism depended only upon the excessive phosphate excretion can no longer be upheld.

Thanks to the better understanding of the pathologic physiology of the metabolic changes due to hyperparathyroidism, it is no longer necessary to use the formula $\frac{Ca \times P}{pH} = K$ for the explanation of the hypophosphatemia in this condition. This is certainly advantageous since the general applicability of this formula is at least doubtful. As an example, sprue-like conditions and other kinds of fatty diarrhea may be mentioned.

In addition, Albright's investigations have considerably widened the concept of hyperparathyroidism. Originally hyperparathyroidism was identified with generalized fibrocystic disease or Recklinghausen's bone disease. It has now become evident that if the food is rich in calcium, hyperparathyroidism may not cause skeletal deformities but may lead only to the formation of renal stones, or to renal insufficiency, or to gastrointestinal syndromes, or to a diabetes insipidus-like syndrome, or even to depressed mental conditions.[19] This holds especially true in the United States where the average daily calcium intake is very high indeed. In this part of the world hyperparathyroidism results more frequently in nephrolithiasis than in generalized osteitis fibrosa.

Mechanism of the Hyperphosphaturia Caused by Parathyroid Hormone

The foregoing evidence would seem to explain satisfactorily why hypercalcemia, hypophosphatemia, hypercalciuria, and also hyperphosphaturia, occur in hyperparathyroidism. Many authors disagree about the mechanism which causes the excess of phosphate excretion in the urine, under influence of parathyroid hormone injections. Albright and Ellsworth[19] originally assumed that the threshold value of phosphate excretion by the kidney decreased under influence of parathyroid hormone. Later Albright's school postulated that parathyroid hormone alters the state of the phosphates dissolved in the body fluids so as to make them more readily excreted by the kidneys.

Both these explanations appear unsatisfactory.

Before discussing the results of the animal experiments which have been performed to explain this phenomenon, it should be realized that these experiments are undertaken to explain metabolic changes observed in chronic hyperparathyroidism in humans. Until now it has remained impossible to produce all the signs of chronic hyperparathyroidism in animals. Repeated injections of dogs and rats with parathyroid hormone, prepared from parathyroids of cows, are of no avail because after some time the hormone loses its efficacy – possibly because antibodies against the hormone are formed. This also often happens when humans are treated with injections of parathyroid hormone for a long time.

However, even short-term experiments with parathyroid hormone in animals often produce results which differ from observations made in humans. In contrast to the observations of Albright and his associates in humans, parathyroid hormone injection in dogs usually causes an increase of the serum phosphate and sometimes even a decrease of the phosphate excretion! Only Handler[20] has been able actually to produce hypophosphatemia combined with hyperphosphaturia in dogs by injections of parathyroid hormone. It is hardly surprising that such difficulties are encountered. The physiology of the kidney of man and dog differs so much that many of the similarities in metabolism of humans and canines should be considered as only coincidental. Acetonuria in dogs always indicates the dog's liver is free of glycogen but when the diabetic patient dies in acetonemic coma, large amounts of glycogen are still present in the liver. The dog's liver is not able to synthesize hip-

puric acid which is formed in large amounts in the human liver. The isolated dog's kidney forms cinnamoyl glycine from cinnamic acid and glycine because in the dog's kidney no oxidation of cinnamic acid to benzoic acid takes place.[21] The latter oxidation is easily performed by the human kidney. This is closely connected with the fact that the isolated human kidney oxidizes phenylpropionic acid to benzoic acid whereas in the isolated dog's kidney only a partial oxidation of phenylpropionic acid to cinnamic acid occurs. And the fact that dogs – with the exception of the Dalmations – excrete allantoin instead of uric acid in the urine is only too well known!

After all these reservations, mention should be made of the experiments of Harrison and Harrison,[22] from which it appeared that parathyroid hormone causes a decrease of the reabsorption of phosphates in the kidney tubules. In this way the hyperphosphaturia caused by parathyroid hormone could easily be explained. These experiments, however, have been criticized because the plasma phosphate concentrations employed in the experiments of Harrison and Harrison varied only over a very narrow range. This may well have been an advantage since in humans with hyperparathyroidism the serum phosphate – usually ranging from 2.5 to 2 mg. per cent–also deviates relatively little from the normal serum values of 3-4 mg. per cent. Nevertheless, some physiologists feel that it would have been preferable if the reabsorption of phosphates in the renal tubules in normal and parathyroid-treated animals had been investigated over a wide range of serum phosphate levels.

Fay and her associates[23] could not confirm the results of Harrison and Harrison. They measured the phosphate-creatinine clearance ratios in dogs and found that some fourteen hours after administration of large doses of parathyroid extract, no interference with tubular reabsorption of phosphates could be elicited. Jahan and Pitts came to comparable conclusions.[24] They observed that about twenty hours after subcutaneous injection of parathyroid hormone to two dogs the calcium content of the serum had risen from 9.6 to 14.1 mg. per cent. However, in contrast to the findings in humans, neither the inorganic phosphorus of the serum nor the urinary excretion of phosphates had changed significantly. Thus, they could find no evidence of an inhibition of the reabsorption of phosphates by the cells of the renal tubules under influence of parathyroid hormone. The original observations of Albright and Ellsworth on increased phosphaturia after injection of parathyroid hormone were

made immediately after administration of this hormone, the experiments of Fay and associates and of Jahan and Pitts were made fourteen and twenty hours respectively after such injections. Handler and associates[20] therefore restudied the tubular reabsorption of phosphates in animals during the first four hours after injection of parathyroid hormone. Large doses were given – 20 units per kilogram of body weight – comparable to the doses used by Jahan and Pitts. Handler and his associates found that after intravenous injection of the hormone usually no hypophosphatemia or hypercalcemia could be elicited. During the first four hours after subcutaneous injection of parathyroid hormone they obtained data which closely resembled conditions as seen in chronic hyperparathyroidism. The urinary excretion of phosphate of these dogs increased significantly, the serum phosphate actually declined from 5.2 mg. per cent to 4 mg. per cent, the serum calcium increased between 0.9 to 2 mg. per cent. Handler and his associates observed that the increase of the phosphaturia was due partly to increased glomerular filtration, partly to decreased tubular reabsorption. In the later phase of the four hour experiment, the decrease of the tubular reabsorption alone accounted for the increase of phosphatase in the urine.

A warning not to exaggerate the importance of the results obtained in acute experiments was sounded by Hogben and Bollman.[25] They showed in an elaborate study that during immobilization of normal control animals the maximal phosphate reabsorption of the renal tubules gradually declined spontaneously. This decline may amount after three to four hours to 25 to 50 per cent of the initial phosphate reabsorption. The response of the tubules to submaximal loads is subject to even greater variations. After accounting for these experimental errors, Hogben and Bollman actually did find an increase of the phosphate excretion under influence of parathyroid hormone which, however, was only caused by the increased filtration rate. They also emphasized that changes of the calcium content of the serum could inhibit phosphate reabsorption and that therefore an increased tubular phosphate reabsorption found in the thyroparathyroidectomized dog might be the result of the hypocalcemia and not be the direct effect of the absence of parathyroid hormone.

Thus the opinions of the modern physiologists differ widely. Whether the increase of phosphates in the urine of hyperparathyroid patients is due mainly to the increase of glomerular filtration (Hogben and Boll-

man) or whether decrease of the reabsorption of phosphates by the renal tubules plays an important role still remains to be proven. Harrison and Harrison[22] and Handler[20] are in favor of this assumption, Fay, [23] Jahan and Pitts[24] deny this possibility. Even if a decrease of phosphate reabsorption actually occurs, it is not certain whether this phenomenon is due to a direct influence of parathyroid hormone on the tubules or whether it is caused by hypercalcemia, irrespective of the cause of the increase of serum calcium (Hogben and Bollman).

Since parathyroid hormone may influence the reabsorption of phosphates in the kidneys it would be interesting to know whether the reabsorption of calcium in the renal tubules is also modified by this hormone. This question is difficult to answer because it is virtually impossible to determine the amounts of calcium ultrafiltered by the renal glomeruli. Part of the calcium of the serum is present in ultrafiltrable form, and in part it is bound to protein. This partition of serum calcium into an ultrafiltrable and a non-ultrafiltrable fraction varies with the pH and the CO_2 content of the serum. Ultrafiltration of the serum outside of the body will therefore not always answer the question, how much of the calcium is ultrafiltrable. Jahan and Pitts,[24] taking all possible precautions during ultrafiltration, came to the conclusion that at least in dogs twenty hours after administration of parathyroid hormone, reabsorption of calcium by the tubules was not inhibited.

Comments

Although the biochemical and clinical syndrome of hyperparathyroidism seems to be explained adequately by experimental evidence, nevertheless, several points will need further clarification.

It is generally accepted that the decalcification in Recklinghausen's bone disease is diffuse and attacks all parts of the skeleton. However, Albright correctly emphasized that one of the very first signs of hyperparathyroidism is manifested by decalcification and disappearance of the lamina dura of the teeth. This is not only the case in patients with far advanced skeletal lesions. Even in patients where hyperparathyroidism presents with excessive formation of renal stones, or nephrocalcinosis, or with the appearance of a giant cell-tumor, but where roentgen evidence of a generalized disease of the bones is non-existent, the lamina dura has already disappeared. Among the patients with hyperparathyroidism we have encountered, there was only one in whom the lamina

dura could be demonstrated roentgenologically in the face of slight generalized decalcification. In this case histologic examination of a biopsy of the jaw confirmed that the lamina dura had remained intact.[19a] This is in sharp contrast with the findings in post-menopausal osteoporosis or in hypoestrinism where the bone of the jaws may be demineralized markedly although the lamina dura usually remains clearly visible. This predilection of the decalcification of the lamina dura of the teeth is difficult to explain and until now has not been elucidated by experimental evidence.

It also remains unexplained why, in contrast to the frequent occurrence of decalcification of the skeleton in hyperparathyroidism, no sclerosis of the skeleton develops in hypoparathyroidism, although in the latter disease hardly any calcium or phosphorus is excreted in the urine. It is true that the interesting experiments of Weinman and associates[26] seem to indicate that the osteosclerosis present in *ia* rats and in grey-lethal mice might be connected with a retarded development or dysfunction of the parathyroid glands. However, as far as human pathology is concerned, patients born with idiopathic hypoparathyroidism may live for many decades, and roentgen surveys of their skeletons do not indicate that the bones are abnormally rich in calcium phosphate. It is evident that the deposition of apatite in the bone matrix does not depend alone on the amount of calcium phosphate retained in the body and that there must exist special regulating mechanisms for bone formation which still escape us. It might then be wise not to explain all phases of decalcification of bone by a negative calcium balance alone – even though this seems an important part of the picture.

The interesting clinical syndrome described by Albright and his associates[27] as pseudohypoparathyroidism, has evidently little in common with hypoparathyroidism. It is true that hypocalcemia exists in these cases but the parathyroids are normal. Albright has explained this remarkable syndrome by assuming that the end organs which regulate the calcium metabolism do not respond to parathyroid hormone. This explanation scarcely accounts for the shortening and broadening of one or more of the metacarpal and occasional metatarsal bones, frequently seen in these patients. These lesions probably are genetic in origin and are not connected with hypoparathyroidism. Such anomalies are comparable to bone changes seen in achondroplasia and especially in dyschondroplasia. Murk Jansen had long ago discussed comparable abnor-

malities of bone growth. In his opinion, they are due to anomalies of tubulation, that is, absorption of metaphysial bone tissue during the growth of bone.

Summary

The biochemical syndrome as seen in hyperparathyroidism can be explained by the excess of parathyroid hormone production. This stimulates proliferation of the osteoclasts of cancellous bone and thereby increases the erosion of bone trabeculae. The ensuing liberation of large amounts of calcium phosphate causes hypercalcemia and hypercalciuria. Although large amounts of phosphates are liberated from the skeleton, hypophosphatemia instead of hyperphosphatemia results, because at the same time parathyroid hormone so strongly stimulates phosphate excretion by the kidney that the serum phosphates not only do not increase but actually decrease. Whether this hyperphosphaturia is simply due to increased glomerular filtration or to decreased phosphate reabsorption by the renal tubules or to a combination of these two conditions, is still a contested point in renal physiology. In addition no agreement has been reached whether a decreased phosphate reabsorption would be due to a direct influence of parathyroid hormone on the tubules or whether hypercalcemia, irrespective of its cause, can decrease tubular reabsorption of phosphates.

The differences in the renal function of man and dog are emphasized in order to sound a note of warning to prevent the premature application of experimental data to the solution of these clinical and pathologic chemical problems.

There is also reason to believe that the spread of the decalcification of the skeleton in hyperparathyroidism may depend not only upon a negative calcium and phosphorus balance, but also upon other as yet obscure mechanisms.

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RELATIONSHIPS IN MEDICINE BETWEEN ASIA AND THE WESTERN WORLD*

EDWARD H. HUME

SEVENTEEN years ago this month, Professor Allen O. Whipple read a memorable paper before the Section on Historical and Cultural Medicine, on the "Role of the Nestorians as the Connecting Link Between Greek and Arab Medicine." He told us how the Aramean priest Nestorios became Patriarch of Constantinople in 428 A.D., how he came into conflict with the orthodox fathers of the church because of his heretical doctrines, and was deposed at the Council of Ephesus in 431. It was his followers who came to be called Nestorians. They first moved to Edessa in upper Mesopotamia, east of the Tigris, and, later, settled in southwestern Persia at Gondi-Sapor. Here the Persian school of medicine flourished from 530 A.D. until the end of the tenth century. The diplomates of that school treated the Prophet and the first Khalifs. It was from Gondi-Sapor that medical emissaries moved west to Salerno where the first organized medical school in Europe grew up. Here indeed was an early relationship in medicine between Asia and the Western World. After Salerno, Bologna was founded and, after that, Padua.

It was a hard world when the Christian era began. Long before the reign of the emperor Augustus, earlier Asian kings had been seeking to exploit the whole world. One is reminded of Nebuchadnezzar, the Babylonian sovereign, who erected a golden image and sought to force people of every race to fall down and worship it. There were gracious kings as well, like Asoka of India, who ruled in the Mauryan Empire to the far north, ascending the throne in 273 B.C., fifty years after Alexander the Great had died in Babylon. He set a pattern for health that has made historians speak of his reign as the golden age of Indian medicine. Asoka's system, based on Buddhist teaching, laid tremendous emphasis on the sanctity of all life. He reduced the allowance of flesh for the

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royal household "from thousands of animals daily to two peacocks and a deer, and even this amount was soon abolished." Our good friend Dr. Albert Schweitzer, with his deep reverence for life, would have been a great admirer of Asoka. He laid out medical gardens everywhere and grew in them healing herbs imported from other lands. Travelers were well cared for, banyan trees were planted along the great highways to give shade to man and beast, and wells were dug by the roadside at frequent intervals.

Asoka was the first builder of charitable hospitals for man and animals. These early hospitals preceded by four or five centuries the first hospitals on Christian foundations. They stood as a sign of visible and practical concern for human suffering.

Even before the reign of King Asoka, when Alexander the Great invaded India in February, 326 B.C., he found Hindu physicians and surgeons so skillful that he retained some of them at his court for emergencies. The duties of an army surgeon were noted as these: "When the king goeth forth with his army, he shall take with him a skillful physician, who must see to the food, water, wood, and places of encampment. If he find poison he must remove it, and so save the army from death and destruction. His tent shall be near the king's tent, and there shall be a flag over his tent, so that the sick, poisoned, or wounded may find him quickly." During the first five hundred years of the Christian era there lived Charaka, the most eminent of the early Hindu physicians; Susruta the most famous of all Indian surgeons; and Vagbhata. These three were known as "the three great medical authorities of the present cycle of the universe."

Some of the early Chinese rulers, like Wu Ti of the early Han dynasty sent out expeditions both to subdue neighboring tribes and to get priceless commodities for the Middle Kingdom. "Go and fetch them," they were ordered. And what they found when they fared forth enriched the rest of the world. They helped diverse traditions and cultures to meet each other. It was this mutuality that proved one great step in advance for the World Planners after World War I. They realized that to win and maintain peace there must be a meeting of the minds and hearts of peoples. Problems of suffering and unemployment are urgent, to be sure; but relief as such, no matter how generous, does not lead to lasting good will unless there is also present a mutual appreciation of one another's cultures.

This is the principle underlying what we speak of today as the Point Four Program, which is concerned far more with Time and People than with Things and Money.

In the great Asian nations of China, India, and Iran, the main roots of the national medicine are cultural. They are tied into the social fabric, into the art and literature of each nation. These roots of the national medicine thus prove to be a mirror of the life of the people. Thus, in China, these social relationships are evident in each period of history. In pictures or sculptures of the forefathers of Chinese medicine, whether in temples or elsewhere, the relationship of medicine to the social structure of the nation becomes evident. Medicine throughout Asia has a social philosophy and a metaphysical approach that we of the West know little of and scarcely appreciate.

It was on a cold Sunday morning, February 22, 1784, that a curious crowd gathered on a pier in New York City to watch the *Empress of China* hoist sail, fire a thirteen-gun salute and sail slowly out to sea, bound for China.

China! For centuries the name had stood for riches and romance, for silks and tea, for gold and jade and fine porcelain. Now for the first time a ship flying the American flag was leaving to enter direct trade with that far land of the Orient. No wonder the crowd regarded the event as memorable.

The more we get to know of the real China, not the Communist-dominated government of today, but the true Chinese people, the more eager we shall be to discover the full extent of our debt to them, in art and literature, in philosophy and in medicine.

It was not only American indifference that lessened the opportunities for contact between China and America but excessive Chinese self-approval as well. In 1722 the reign of K'ang Hsi ended. Ten years later his grandson, Ch'ien Lung, became the Emperor. Near the end of his reign the British sent an envoy to China asking the ruler to recognize an ambassador who might live in Peking and look after British interests throughout China. Ch'ien Lung made this very high-sounding reply:

"Our dynasty's majestic virtue has penetrated into every country under Heaven, and kings of all nations have offered their costly tribute by land and sea. As your Ambassador can see for himself, we possess all things. I set no value on things strange or ingenious and have no use for your country's manufactures. This, then, is my answer to your re-

quest to appoint a representative at my court, a request contrary to our dynastic usage, which would result in inconvenience to yourself."

The more we inquire, the more we shall understand how it was possible that, over the gateway of one of the northern cities of China, centuries ago, armies coming in from Mongolia read the inscription:

"ENTRANCE TO CIVILIZATION"

We of the Western world have scarcely learned to think of the Orient as one of the great centers of civilization in the universe.

Consider the invention of paper:

"In ancient times in China writing was generally on bamboo or on pieces of silk which was then called *chih*. But silk being expensive and bamboo heavy, these two materials were not convenient. Then the privy counsellor, Ts'ai Lun, thought of using tree bark, hemp, rags and fish-nets. In the first year of Yuan Hsing (A.D. 105), he made a report to the Emperor on the process of paper making and received high praise for his ability. From this time paper has been in use everywhere and is called 'the paper of Marquis Ts'ai.' "*

When Thomas Carter first came in contact with the Chinese farmers he was amused to find that their children knew more about the seasons and various harvests, about grains and animal husbandry, than he did with his Princeton Phi Beta Kappa, cum laude, and three years of graduate studies. He found in these simple folk who had never looked inside a book, a veneration for learning which well matched that of his own Scottish ancestors. He came to feel that there was as great a need for an interpretation of the civilization of the East to the West as for the West to have its interpreters in the East.

My own first voyage up the Yangtze River, in 1905, remains unforgettable. It was the first of many voyages of discovery. We sailed from Shanghai early one morning and were out on the broad stream before noon. Vessels lined both sides of the river and the captain called me up on the bridge to point out their variety. "That large ship," he said pointing to a huge junk, "is carrying salt up into the interior. Those other junks headed downstream are bringing digitalis from the western province of Szechuan down to the coast to be reshipped to America and Europe." He went on to tell me that after tinctures and tablets had been made they would be sent out and sold in China. Every year in China, I discovered unexpected varieties of Chinese drugs, some of

* Carter, T. F. *The invention of printing in China.* New York, Columbia Univ. Press, 1925, p. 3.

them herbs, some of them minerals, and others of animal origin. It took the Chinese many centuries to become familiar with the flora of their own country. Their knowledge of species increased from the early days onwards. The original herbal was prepared by Shen Nung (legendary date B.C. 2952) and listed 250 plants with their uses. In fifty-five centuries this list grew to 816. This herbal of the 16th century was regarded so important as to make it a fitting offering to one of the great Emperors of the late Ming dynasty. The expansion of knowledge was brought about in certain definite ways. In every part of the land there was continued observation of local flora and fauna and a study of their uses in the service of man. There was also continuing description of wild and cultivated things made by travelers and writers. Yet the understanding of the flora of China still remains incomplete. One of our foundations has just made a grant to the Arnold Arboretum at Harvard to provide for a fresh, extensive study of China's flora.

Those of you who have crossed Nebraska by the Union Pacific Railroad will doubtless remember a little local stop, Alfalfa City, and may have wondered about the origin of that plant. It was described by the late Berthold Laufer, in his massive volume "Sino-Iranica." He tells of a military mission, B.C. 138, which was designed to subdue the Huns but which also brought back to China two of its great vegetable treasures, the grape and alfalfa. The fine horses of Iran had thrived on alfalfa, and the leader of the expedition, General Chang Ch'ien, who had obtained possession of a large number of the Iranian thoroughbreds for his master, was wise enough to take enough alfalfa seed to plant in the palace grounds. The general also recognized the great value of the grape as a food and as a source of excellent wine. This was introduced into the province of Shansi where wine-making remains an essential part of the local industry. Laufer continues to describe plants which are not of west Asian origin: the walnut, coriander, pepper, cucumber, chive, carrot, and many others. By studying the prefixes to the names we can discover how many botanical elements were brought from China to the west by the overland route: the peach, apricot, ginger, rhubarb, tea, cinnamon, as well as saltpetre and kaolin.

Many of the flora were introduced into China from Arabia, and because of their Muslim origin have the prefix *hui*. Thus, both fennel and anise, as well as chive, carry a prefix indicating their Arabic and Muslim origins. These stories of plants bring us not only medical his-

tory but stories of culture drift. Thus, the cocoon of the silkworm was brought to Europe by monks in their hollow staffs.

China sent many articles of vegetable and mineral origin to India, such as camphor, alum, arsenic, etc. These are recorded in Buddhist works. We read that a large group of Indian Buddhist monks went over to China in B.C. 217. While there may be a dispute as to the actual date of the introduction of Buddhism into China, we know that not later than the first century A.D. Buddhist monks came over. The Chinese themselves have reliable records of their own pilgrims who traveled overland to India, reputedly before 639 A.D. In the last named year it was the pilgrim Hsuan Tsang who made the most memorable journey. All these travelers have recorded observations of the flora and fauna of the places which they visited. Thus, we have records of the obvious association that Buddhism had with such things as sandalwood and lotus. The sacred *Ficus religiosus* was the tree under which Buddha sat and preached. In China there are many centers where this p'u t'i tree is honored. This name comes from the Indian word Buddhi or wisdom.

In the early days religion and medicine were closely associated and we find the arts and crafts absorbing many of the flora which might be used for dyeing. Opium (a-fyun) was introduced into China from Arabia or Iran, perhaps as early as the Sung dynasty (900-1200 A.D.). It is entirely possible however that a narcotic like opium was known in prehistoric times, associated with the secret rituals of the early tribes. It is probable that initiation was accompanied in some countries with the use of drugs. Opium was undoubtedly known to the early travelers.

While numerous noteworthy discoveries for the healing of the sick have been made during recent years, medical science still owes much to the people of the past for the accumulated knowledge of many remedies and cures. Primitive medicine was nearly always empirical. Sometimes it was superstitious but often was based on keen observation. Such observations when confirmed and thoroughly experimented with then become sound principles in modern medicine. An example of this is to be found in the prevention of smallpox. Many centuries before Edward Jenner introduced vaccination in 1796, the inoculation of smallpox pus had been known in India and China, in Arabia, and in Africa. Still another example of sound observation is found in the introduction of the foxglove or digitalis. The leaves of the plant had long been known in China to diminish body fluids in dropsy, and it was in 1775 that William

Withering started its use in medical practice in England. Doctor Withering found an old family recipe which led him to investigate the curative values of digitalis, which has now become an indispensable drug in relieving the symptoms of certain cardiac disorders.

In Chinese civilization there is a very rich flora of curative materials. Some of these, such as camphor, cinnamon, anise, and rhubarb, have already been admitted to modern pharmacopoeias. There are however many other drugs in China which were believed in that country to have unlimited curative value but which have never been subjected to careful critical inquiry in the West. It is such investigations that are called for now and are bound to bring fruitful results. The recent introduction of *Ma Huang* into Western medicine is a good illustration. *Ma Huang*, botanically Ephedra sinica, is an herb that grows wild on the northern and western frontiers of China. It has been known in Chinese medicine since antiquity. At least 3000 years ago Shen Nung tested this drug and admitted it to his ancient herbal. The drug is believed to produce sweating, reduce fever, stimulate the circulation and relieve cough. It has long been an ingredient of several famous prescriptions, one of them used in the treatment of a disease similar to typhoid.

Ma Huang (Ephedra sinica) without nodes—10 catties Apricot Kernels (Prunus armeniaca) blanched—4 sheng Rhubarb (Rheum officinale)—1¼ catties Snow Water

Detailed instructions were given for making an extract of the above crude drugs and finally dividing the mass into pills. The efficacy of this remedy was believed to depend on the power of *Ma Huang* to produce perspiration. Chinese always believed that perspiration was a means of reducing fever. Usually, *Ma Huang* was prescribed with other crude drugs and made into a decoction, and ordered to be taken by the patient as such. Prior to 1887 little else was known about the status of this ancient drug. It was a Japanese chemist who in 1887 isolated the pure principle which has since been called ephedrine. Many Japanese scientists discovered that this drug would dilate the pupil but they did not recognize other aspects of its clinical use. For the next thirty-five years scientists were largely concerned with determining the chemical composition of *Ma Huang*. They established its structural formula and achieved a synthesis, but went no further.

In 1923, Drs. Carl F. Schmidt and K. K. Chen, while working at the Peking Union Medical College, began to study a group of potent drugs

suggested to them by a Chinese druggist, in whose list *Ma Huang* was found. So the two scientists bought a small sample from a Chinese drugstore, made a decoction of the drug and injected a portion of it into a narcotized dog left by a group of students after their laboratory exercise; they at once observed a prolonged rise of blood pressure. The result of this first experiment aroused their enthusiasm and stimulated them to carry out exhaustive inquiries. They soon found that ephedrine would contract the mucous membranes of the nose. This led to its use in the treatment of rhinitis and hay fever. During the decade ending in 1930 there was a rapid development of publications on ephedrine and a vast increase in the amount of shipments abroad. The ancient drug *Ma Huang* has risen to prominence and many workers in China have now found for themselves a new calling in making annual collections of *Ma Huang*, which is shipped in bales to all parts of the world. It may be safely said that the study of *Ma Huang*, and subsequently of ephedrine, furnishes one more example in medicine where a traditional belief has become a rational therapy. Moreover, it represents one of the most international types of human endeavor. The crude drug is of Chinese origin but the active principle was isolated by a Japanese scientist. The constitution of ephedrine was explored and established by several Germans and Japanese, while other aspects of the inquiry were achieved by Frenchmen and Austrians. The pharmacological investigations were initiated by Japanese scholars and a thorough study was made by an American and a Chinese. Some of the clinical tests leading to the proper use of ephedrine were made by Americans working with Canadians.

Chinese medicine is really a cultural element in society, a mirror of the people's attitudes; this connection is evident in each period of Chinese history. Thus, three great figures, known as the forefathers of Chinese medicine, are constantly shown together, whether in paintings or in temple images: Fu Hsi, the founder and philosopher; Shen Nung, the one who related agriculture to medicine; and Huang Ti, the Yellow Emperor, who related inquiry and observation to medicine. Fu Hsi is credited with being the author of the *Pa Kua*, the Eight Diagrams. These were revealed, so tradition has it, to Fu Hsi while riding on the back of a supernatural animal that rose from the waters of the Yellow River. These diagrams have been used for at least three thousand years to symbolize the processes of nature, and are a feature of all Taoist dis-

cussions of astrology, alchemy and medicine. In the center of the Eight Diagrams one finds a circle, within which an S-shaped line separates two fish-like shapes, the *Yin* (black) and the *Yang* (white), which represent the primal forces of nature. The whole figure is a charm or talisman, used in a variety of ways to ward off disease and evil spirits. Fu Hsi is to be remembered because he organized the people and taught them how to live securely within a framework of social regulations. He is known as the builder of the life of the people, within which medicine was a necessary element.

Shen Nung, the second of the triad, was known as the Divine Agriculturist. Not only did he examine the soil and teach his people how to till it; but when sickness spread, he searched for remedies ceaselessly, so much so that it became a common saying: "Shen Nung daily tasted a hundred herbs." He laid the foundations of the pharmacopoeias of which China has boasted for some three thousand years.

Hwang Ti, the Yellow Emperor, was the third of the three notables. To him is attributed the *Nei Ching*, Canon of Internal Medicine, a work that is an even greater contribution to China's medicine than his social regulations. The work falls into two parts, the first being named *Su Wen*, Familiar Conversations. These are really dialogues between the Emperor and his able minister Chi Pai. In one of these we read: "The good man in most ancient times held Heaven and Earth in his hand and grasped light and darkness, breathing pure air and preserving the spirit in its perfection, for his flesh was obedient to his spirit. Because of this he was able to attain immortality like that of Heaven and Earth." Another paragraph reads: "The sages did not treat those who were already ill; they instructed those who were not yet ill. . . . To administer medicines when diseases have already developed is comparable to the behavior of persons who begin to dig a well after they have become thirsty. Is not such action too late?"

Chinese medicine is not to be judged merely by its elements of magic and superstition or by its cosmic and animistic theories. It was a reflective philosophical system, always thinking of man in his relationships to the vegetable and animal kingdoms as well as to man and other animals. Rather than being a truly experimental system, the experimental elements in it were only fragmentary and occasional. If the example of those who created its earliest life had been followed, it would have advanced immeasurably; but there appeared in the environment numerous

factors that prevented, rather than facilitated, the spirit of inquiry. Thus, animism was followed by Taoism with its emphasis on alchemy and the search for immortality through transmutation of certain elements, such as mercury into gold. After this came Confucianism, with its ethical emphasis and its strict ceremonial practices. Buddhism followed, teaching asceticism and a future life after passing through an infinite series of punishments. Among the sins for which definite and horrible penalties were provided were the taking of bodies from graves and the desecration of the human frame. None of these factors was conducive to true scientific research.

And yet, though not a land of experimentation, China is a land of learning. Every literary man has received some training in the principles of medicine. Throughout the centuries, medicine has received honor in the thought life of the nation. Every dynastic history, and the annals of every province and county, make mention of local developments in the realm of medicine. It is noteworthy that when Shih Huang Ti, the unifying emperor of China, ruler of the state of Ch'in, "burned the official chronicles of the different feudal states, including The Classic of Poetry (Shih Ching), The Classic of History (Shu Ching), and the discourses of the teachers of the philosophical schools, the only books excepted from his proscription, were those on divination, on medicine, on agriculture and arboriculture, and the official chronicles of the state of Ch'in."

One of the striking facts in Chinese medicine is the emphasis on diet. Beriberi was known in China as early as 2600 B.C. but its dietary treatment was only shown conclusively as recently as 1880. During the Mongol dynasty in China there was an illustrious scholar, Hu Ssu-Hui, who wrote in detail about the dietary treatment of "wet" beriberi and of "dry" beriberi. In his remarkable book "Principles of Correct Diet," each page has an inscription in one corner, "food cures various diseases." The Chinese have been noteworthy among the nations in their descriptions of the way many conditions should be treated; what the diets should be for pregnant and lactating women, for children at different seasons of the year and during various mental states.

Both China and India have contributed to medicine by great stress on careful diagnosis, and on physical therapy. In both countries, their systems of medical thought, while truly philosophical in conception, have led to practical procedures of real value in both diagnosis and

treatment. While it is true that the development of Greek and Arabic medicine formed much of the basis of European thought and teaching, yet the Chinese stream of medical thought, much older than the Greek and Arabic, was proving adequate to the needs of a far-eastern Asiatic civilization. We are only at the threshold of an adequate understanding of this development. It remains for the medical historian to press forward to explore the documents, still at hand for inquiry; and for the pharmacologist to explore the therapeutic values of the hundreds of medicinal substances that have come out of Asia, so that there may be fuller understanding of the Relationships in Medicine Between Asia and the Western World.

CONFERENCES ON DRUG ADDICTION AMONG ADOLESCENTS *

The Proceedings of two Academy-sponsored conferences on teen-age drug addiction may now be obtained in book form. Over 50 experts representing various professions and agencies, each concerned with drug addiction, contributed to a comprehensive approach. Among the points considered: the report of a new drug for the detection of narcotics addiction, the role of education in the prevention of adolescent drug use, and the designation of narcotics addiction as a "disease of deprivation."

Copies of the book, entitled CONFERENCES ON DRUG ADDICTION AMONG ADOLESCENTS, may be obtained from The Blakiston Company, 575 Madison Avenue, New York 22, New York. The price of the book is $4.00.

* Held under the auspices of the Committee on Public Health Relations of The New York Academy of Medicine.

NOTES ON THE HISTORY OF DIABETES MELLITUS, II:

SEARCH FOR THE ANTIDIABETIC PRINCIPLE*

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IN 1889 Joseph von Mering and Otto Minkowski[1] reported that total removal of the pancreas in dogs results in the picture of "real permanent diabetes mellitus, which corresponds in every detail to the most severe form of this disease in man." The pancreatectomized dogs did not only become permanently glycosuric, they also developed excessive polyphagia and polydipsia and marked polyuria; they lost weight rapidly and became cachectic; in some cases there was ketonuria; the blood sugar was markedly elevated and early in the course of this experimental disease the glycogen disappeared almost entirely from the animal's organs.

Von Mering and Minkowski concluded that the diabetes following total pancreatectomy was not caused by a lack of pancreatic juice but was due to a "still unknown function" of the pancreas which was absolutely essential for the utilization of sugar.

This was not the first time that glycosuria had been induced experimentally. Claude Bernard,[2] in 1849, had observed this phenomenon following "piqûre" of the fourth ventricle and von Mering, in 1886,[3] had discovered that dogs developed glycosuria on administration of phloridzin. But in neither instance could one speak of true diabetes, and neither procedure afforded insight into the etiology of human diabetes. However, Bernard's experiment exerted a distinct influence on the thinking of many clinicians and it was long believed that brain tumors and head injuries could cause diabetes (Harley), and for Dickinson diabetes had been a disease of the "nervous system."[4]

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But now the etiology of diabetes mellitus appeared in a new light. Although von Mering and Minkowski's discovery did not explain the nature of the "still unknown function," it established clearly that the pancreas was essential to normal carbohydrate metabolism.

Almost immediately after the publication of von Mering and Minkowski's first paper, Lépine[5] reported that he had been able to confirm their results and at the same time he formulated a "new theory of diabetes" based on the assumption that the pancreas was "not only a gland which produced a secretion which it emptied into the intestine" but that it was "also a kind of blood-vessel gland which passed into its veins . . . the ferment needed by the liver." Pancreas diabetes, according to this theory, was due to lack of the ferment which, Lépine believed, was a diastase.

The first proof of the endocrine nature of the "still unknown function" of the pancreas was given by Minkowski[6] who was able to reverse the diabetogenic effects of pancreatectomy by implantation of a pancreas in a pancreatectomized dog (1892). And in the next year Capparelli[7] found that the glycosuria of experimental pancreas diabetes disappeared almost entirely upon intraperitoneal administration of ground pancreas. This antidiabetic action, Capparelli contended, was due to ". . . a substance which disintegrates rapidly upon extraction from the pancreas. . . ." In the same year (1893) Laguesse[8] advanced, "with all reservations," the concept that the internal secretion of the pancreas was produced by the islands of Langerhans, groups of cells which the latter author had described in 1869. They are ". . . gathered in small clumps" and are "distributed at regular intervals in the parenchyma of the gland." Concerning the nature of these cells, however, Langerhans "conceded freely" that he was ". . . in no way able to offer any explanation."[9]

That the internal secretion of the pancreas stemmed from the "islands" was advocated also by Ssobolew,[10] who based this view on the fact that although ligation of the pancreatic duct resulted in atrophy of the parenchyma, diabetes did not supervene. And in his own experiments he was able to demonstrate, as he had postulated theoretically, that the islands of Langerhans underwent no morphological changes upon ligation of the duct. Ssobolew also observed partial, and in some instances, total disappearance of the islets in 13 fatal cases of diabetes. In continuation of Ssobolew's work, Opie[11] examined microscopically

the pancreas from eleven cases of diabetes, and in four instances "such marked change was found (in the islands) that one could not doubt the relationship of the general disease to the lesion of the organ."

During this period there was also inaugurated the search for the hypothesized antidiabetic principle. By subcutaneous injection of pancreas extract Blumenthal[12] had, in 1898, succeeded in improving temporarily (for two days), the sugar utilization in a diabetic patient. However, the extract had repeatedly caused necrosis at the site of injection, and since he could not overcome this drawback, Blumenthal had felt it necessary to discontinue its use. Nine years later (in 1907) Rennie and Fraser[13] reported marked improvement in five diabetic patients through the administration of an extract prepared from the islets of certain Teleostei. These experiments are especially interesting since in these fishes the islets form organs which are not embedded in the pancreas.

Despite the mass of evidence which had accumulated over the years in support of the pancreas theory of diabetes several authors, foremost among them the famous physiologist Pflüger, contested its validity. Pflüger attacked Minkowski with great vehemence and the ensuing controversy was conducted by both men with utmost acrimoniousness. As late as 1909, shortly before his death, Pflüger wrote: "I am . . . still of the opinion that internal secretion has not been proven to be the cause of pancreas diabetes." And there follows in the next sentence, the most remarkable bit of scientific double talk: "The unproven can nevertheless still be true. That is my standpoint."[14]

In the next year (1910), after the demise of Pflüger, his pupil Leschke[15] placed himself squarely on the side of his "maître" in declaring that the "practical importance of these attempts (to isolate the antidiabetic principle) lies in the fact that through them the pancreas therapy of diabetes has been deprived of every foundation."

In the issue of November 25, 1909 of the "Deutsche Medizinische Wochenschrift"[16] there appeared a paper from the clinic of Minkowski, now professor of medicine in Breslau, in which his assistant Forschbach "confirmed the important fact," that Zuelzer[17] had prepared, "for the first time a pancreas extract which, administered intravenously (in dogs and humans), diminishes sugar excretion for shorter or longer periods." "The injection of small amounts of this preparation," Forschbach continues, "is accompanied in humans by a rise in temperature and

by a symptom-complex indicative of a very severe intoxication." The patients presented a short time after the injection the picture of "truly terrifying prostration. . . ." "These side-effects naturally constitute an insurmountable barrier against the practical use of the extract." "The fear that still more serious things might follow from injection of the pancreas extract has kept me from making further trials in patients."

The weight of Minkowski's name, which stood behind this publication, put an end to Zuelzer's preparation. In retrospect it is safe to surmise that it was, indeed, the "real thing." The observed "very severe intoxication" and "terrifying prostration" were undoubtedly the signs of what today is known as "hypoglycemic shock." Almost a decade and a half had to elapse before another, more successful, investigator could finally report that he had prepared a potent and usable pancreas extract (not without there having been several near misses, Scott,[18] Murlin,[19] in the interim).

The final victory was not the fruit of intensive theoretical preparation nor of sustained and prolonged experimentation. The conception from which resulted the experimental method for the successful isolation of the long postulated antidiabetic principle was arrived at in the course of a few short hours, the actual experiments in which the elusive substance was at last tracked down were conducted during a few short months.

"On 30th October (1920), it so happened," Frederick Banting[20] later related, "that in the early part of the evening I was preparing a lecture on the relation of the pancreas to diabetes, and when the lecture was completed I commenced the perusal of the newly arrived November number of the Journal of *Surgery, Gynecology and Obstetrics.*" This Journal contained an article by Barron [21] on "The Relation of the Islets of Langerhans to Diabetes with special reference to cases of pancreatic lithiasis." "After reading the article . . . I was unable to sleep. There seemed to be in some vague way a relation between the islet cells of the pancreas and clinical diabetes. There seemed also to be a means of attacking the problem of extracting the islet cells by ligating the pancreatic duct. It was not until two o'clock in the morning that I was able to crystallize the idea into a form that would lend itself to experimentation. At this hour I arose and wrote in my notebook the following words–*Ligate pancreatic ducts of dogs. Wait six to eight weeks for degeneration. Remove the residue and extract.*"

Banting then approached Dr. Macleod, Professor of Physiology in Toronto, an outstanding expert on sugar metabolism, with the request that he be given the opportunity to work on his idea in Macleod's Institute. "I shall never forget that first interview with Prof. Macleod," Banting continues ". . . at the end of the interview the Professor asked me what I hoped to accomplish when the best trained physiologists had not succeeded in establishing or proving that there was an internal secretion of the pancreas." Finally Macleod gave his consent. "Work was commenced on the 16th of May 1921. It was arranged that I should have ten dogs and the use of the laboratory for eight weeks. Mr. Best and Mr. Noble were appointed as assistants, each to give four weeks. They tossed a coin to decide who would give the first four weeks, and Mr. Best won the toss. At the end of the four weeks, however, Mr. Noble did not return and Mr. Best stayed with me."

"On the 27th July we had a depancreatized dog and we decided to begin treatment."

When early in 1922 the results of Banting's investigations were published,[22] ". . . The medical and scientific world was thrilled . . .", wrote Murlin.[23] "One of us," he added, "localized this thrill very near the solar plexus." In 1912, he and his co-workers had carried out and then abandoned experiments with pancreas extracts which, from the vantage point of 1922, had to be regarded as having contained "insulin."

And in the meeting of the Société de Biologie, in Paris, on December 23, 1922, Gley[24] asked that a sealed envelope which he had deposited with the Society in 1906 be opened and its contents read. In this envelope was a paper entitled "Sur la Sécrétion Interne du Pancreas et son Utilization Thérapeutique" in which Gley described a pancreatic extract, the injection of which had markedly diminished the symptoms of experimental pancreas diabetes in dogs. The concept of these experiments had originated in the 1890's but Gley had not been able to start working on them until about 1900 ". . . because of other work in which I was engaged. . . ." The diabetes experiments were again put aside, Gley contenting himself with the deposition of their results in a sealed envelope!

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SECTION ON MICROBIOLOGY

WEDNESDAY EVENING, JANUARY 21, 1953

THE VARIABLE CLINICAL MANIFESTATIONS OF LEPTOSPIROSIS*

THEODORE E. WOODWARD, R. S. DIAZ RIVERA
and
JOHN A. HIGHTOWER

THE PROTEAN MANIFESTATIONS OF LEPTOSPIROSIS

INTRODUCTION

WEIL[1] in 1886, vividly described several human cases of leptospirosis. The classic disease, since the year of his observations is known as Weil's disease and his description of icterus, fever, hemorrhagic tendency, renal, hepatic and vascular failure with a high fatality serves as a basis for present day reference. Years later, in 1915, Inada[2] identified the causative microbe as a spirochete which was subsequently named a leptospira by Noguchi.[3]

Modern bacteriological research methods have complicated the picture through the identification and differentiation of many strains of leptospira shown to infect man. Unlike the classic entity, laid down by Weil, leptospiral infections now compose a multiplicity of separate diseases whose etiological, epidemiological and clinical features vary considerably. The pattern of events as described by Weil is reenacted on wards throughout the world today but emphasis must now shift to the great diversity of the clinical manifestations if we are to suspect and identify the disease.

The present paper will describe the variable clinical manifestations

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of the human varieties of leptospirosis known to be present in North America.

Common North American Types

Following the lead of Australian, European and oriental investigators, human cases of L. icterohemorrhagica, canicola and pomona have been identified in the United States.[4, 5] Recently recognized in this country is Indonesian leptospiral infection (L. bataviae)[6] capable of causing diseases as severe as the classical Weil's type. At Fort Bragg L. autumnalis has been isolated from soldiers who contracted the previously unidentified diseases of pretibial fever.[7]

The application of modern methods in the investigation of a recent human outbreak of leptospirosis in Puerto Rico has extended the knowledge of the disease on this island.[8,9] In addition to L. icterohemorrhagica known to be a cause of human disease, five additional types have been isolated and identified during studies of an epidemic in 1950-1952.[8, 9]

Clinical Description

Classical Weil's Disease (L. icterohemorrhagica): After an incubation period of about eight days, the disease characteristically begins with a rigor and fever. The pyrexia of the classical case continues between 102° to 104° F. for about eight days and falls by rapid lysis. Sudden toxemia, weakness, intense unrelenting headache and myalgic pains of the legs, back, neck and abdominal muscles appear during the early days. The extreme muscle tenderness is a characteristic clinical feature. Arthritic pains may be intense. Gastrointestinal unrest manifested by nausea, vomiting and diarrhea are noted frequently. A confused state of mentality may occur earlier in this disease than in other common infectious diseases.

A tendency to hemorrhage may occur during the first week of illness with gastrointestinal bleeding or hemorrhagic diathesis of the skin, conjunctivae and mucous membranes. Hyperemia and pericorneal injection of the conjunctival vessels are characteristic quite early in the illness and are often pathognomonic of leptospirosis. The conjunctival reaction is usually without secretion and may persist for several days. Not uncommon as eye manifestations are iritis, iridocyclitis and uveitis. These complications which occur usually in convalescence have a reasonably favorable prognosis. An exanthem similar in some respects to scarlatina or

German measles is not uncommon and occasionally the lesions may assume a petechial character.

The circulatory status may be likened to the rickettsioses with respect to hypotension and peripheral vascular weakness often of shocklike degree.

Jaundice, when it occurs, appears usually at the end of the first week of illness simultaneously with the defervescence. It may intensify rapidly and persist for a month or more. Fatalities occur among the jaundiced but the intensity of icterus is not necessarily of prognostic significance. Concurrent with the appearance of icterus is the development of hepatomegaly. Splenomegaly cannot be considered a characteristic feature.

The renal, in addition to the hepatic and circulatory manifestations, constitute by far the most helpful prognostic signs. Albuminuria is consistently present in the severely ill. Oliguria, and ultimately anuria, mark the serious cases and fatality may result from the renal involvement. Circulatory failure and hypotension certainly accentuate the azotemia by reducing glomerular filtration. A sudden diuresis may be considered a favorable omen and fortunately after recovery, permanent renal damage is uncommon. The hepato-renal manifestations occur most frequently during the second week of disease after the temperature has reached normal levels.

Not infrequently the neurological manifestations may dominate the clinical picture. In addition to cephalgia, meningitic symptoms frequently appear. Meningism may be extreme, spinal fluid pressure is often increased and a pleocytosis, composed principally of lymphocytes, commonly encountered. The meningitis usually subsides uneventfully although troublesome neuritis may ensue.

Leukocytosis and a hypochromic anemia represent the more usual alterations of the hematological picture.

Death occurs in approximately 30 per cent of the jaundiced or in patients classified as severely ill. Occasionally death may ensue during the early stages of the disease as a result of vascular collapse or hemorrhage from the gastrointestinal tract. Usually the patient succumbs in the second week of illness from uremia. The controlling features, therefore, are the stability of the renal, hepatic and vascular systems.

Mild Case (L. icterohemorrhagica): Illness in the non-icteric case is characteristically milder and invariably terminates favorably. The course of fever is approximately five to seven days, headache and myalgic signs

are present but less intense than in the classical form. Hemorrhage from the intestine, mucous membranes and skin are much less common in the milder case and congestion of the conjunctivae remains a very characteristic sign particularly during the early days of illness. As a rule, when the temperature reaches normal levels, the usual signs of toxemia rapidly abate. Furthermore, the renal and vascular complications do not occur. Conversely, the meningeal features of leptospirosis may accompany the mild case and occasionally run a protracted but benign course.

A variable clinical course is seen, therefore, in patients infected with L. icterohemorrhagica and it is possible that 50 per cent or more of the cases of this category may be of the mild type. Fatalities in the jaundiced are approximately 30 per cent and are caused by hemorrhage, circulatory or renal failure. Leptospiral meningitis and eye complications such as iritis or optic neuritis are encountered in mild as well as in severely ill cases.

L. canicola: Leptospiral infections contracted from the dog are essentially similar to the classical Weil's type. Jaundice is very infrequent and meningeal symptoms as well as ocular signs occur.[10]

L. pomona: The agent of swineherd's disease, first identified in Pomona, Australia, was given its name of L. pomona by Derrick[11] in 1942. The clinical manifestations resemble the mild form of Weil's disease with pyrexia of about seven days and a very low incidence of icterus and death. One of the frequent findings of human L. pomona infections is the high incidence of aseptic type meningitis.

In this country Schaeffer[12] has reported the clinical findings among a group of children and young adults who contracted the disease following bathing in a local swimming hole in Alabama. Among twenty-six patients, fever, chills, headache, meningismus and pain in the back were uniformly encountered. Arthralgia and myalgic pains were found in a high percentage whereas nausea, vomiting, constipation and diarrhea were less frequent. Less than one-half of the patients complained of photophobia or showed signs of conjunctival irritation. None were jaundiced or showed signs of hepatic or renal involvement. A noteworthy finding in this well studied series was the presence of signs of aseptic meningitis in six of the twenty-six patients who demonstrated a pleocytosis of lymphocytes and increased intracranial pressure. Beeson and others[13, 14] have likewise incriminated leptospirosis as a cause of approximately 10 per cent of those illnesses presenting as benign serous-type

meningitis. Therefore, leptospirosis must be considered as a possible etiological cause along with lymphocytic choriomeningitis, mumps, herpes, poliomyelitis, coxsackie disease and the various neurotropic encephalidites when spinal fluid containing lymphocytes is present.

L. bataviae: The Indonesian form of Weil's disease has been detected in the United States and Puerto Rico.[6] The clinical features are similar to classical leptospirosis of the icterohemorrhagic type.[10] The variability between mild and severe cases, incidence of jaundice, renal and vascular complications and death are roughly comparable.

L. autumnalis (Pre-tibial Fever): Leptospirosis caused by L. autumnalis has been recognized in Japan as a mild febrile disease of about seven days duration characterized by slight icterus in a small percentage of cases and a low fatality rate.[15] In 1943 Daniels and Grennan[16] described a dengue-like illness of unknown etiology among soldiers at Fort Bragg, North Carolina. The disease, of short duration, was characterized by moderate prostration, fever, splenomegaly and a rash peculiarly localized to the anterior aspects of the legs which gave rise to the name pre-tibial fever. A multiplicity of laboratory tests failed to reveal the nature of this disease. Tatlock[17] in an extensive study adapted the unknown agent thought to be a virus to various experimental animals and also to fertile hens eggs. He successfully reproduced the characteristic signs and symptoms of the Fort Bragg illness in human volunteers.

Recent research investigators of the Army Medical Research Graduate School[7] have successfully identified the causative agent as a leptospira similar immunogenically to L. autumnalis. Further studies of the sera from patients with this illness revealed high antibody titers to antigen prepared from this strain.

Additional Protean Features

Occasionally a febrile course of four to six days duration with a saddle-back trend similar to dengue fever is noted. Furthermore, it is not unusual for the temperature to continue in some cases during the early days of the icteric stage, up to the tenth to twelfth day of disease. A febrile relapse with a return of the usual objective and subjective manifestations is not uncommon occurring one to two weeks after the initial defervescence. A localized pneumonitis accompanied by the expectoration of blood-tinged or grossly sanguinous sputum is rarely encountered.

Conclusions

Human leptospiral infections may masquerade as a multiplicity of separate diseases whose clinical features vary considerably. The diversity of the signs and symptoms ranges from the mildness observed in clinical grippal infections to the fulminant pattern not infrequently observed in infectious hepatitis. The variability in severity between the mild and severe types, the meningeal manifestations and complications are discussed.

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*Laboratory Diagnosis of Leptospiral Infections**

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The widespread current interest in the leptospiral infections of man and animals is reflected in a greatly increased demand for leptospiral diagnostic laboratory services. These services, now required at municipal and local levels throughout the United States, have in the past been available only at a limited number of reference laboratories. The cost in specialized equipment, training of technicians, and housing of animals precluded widespread adoption of procedures then advocated for the laboratory diagnosis of leptospirosis. Experience in our laboratories[1] indicates that recently developed and evaluated leptospiral diagnostic methods, within the capabilities of the average laboratory, are of such merit as to warrant their adoption.

In this discussion, it appears appropriate to define the information desired in the laboratory confirmation of the diagnosis of leptospirosis, and to evaluate laboratory methods, in terms of furnishing this information. The essential elements of information are timeliness, specificity and definitiveness. Retrospective diagnoses may furnish the basis of valuable scientific reports but serve only to discourage clinicians seeking assistance on diagnostic problems. Included in specificity is credibility. The laboratory must employ procedures which not only may be capable of confirming or negating the impression of leptospirosis, but which are also sufficiently reliable that credence may be placed in the laboratory's report. By definitiveness in positive reports is meant not only confirmation of leptospirosis per se, but in addition, identification of the infecting leptospires. This is of primary importance in epidemiological investigations and in instances of compensable occupational disease.

Laboratory diagnosis of leptospiral infection may be made by microscopic demonstration of the organisms in tissues or body fluids, by recovery of the organisms in culture or laboratory animals, and by serological demonstration of rises in leptospiral antibody levels.

Leptospires are present in the blood and may also be present in the cerebrospinal fluid during the initial febrile stage of illness. Their disappearance from the blood is associated with remission of fever and the appearance of specific antibodies. This leptospiremic phase is usually limited to the first week of illness. Complement-fixing antibodies are usually first detectable at the tenth day of disease, while agglutinating antibodies usually first reach significant levels at the twelfth day.

Direct microscopic examination of body fluids by darkground illumination offers the theoretical advantage of most rapid diagnosis of leptospirosis. In practice, the difficulty of demonstrating leptospires present in small numbers, often results in falsely negative reports. Even more often, protoplasmic extrusions from cellular blood elements are confused with leptospires, resulting in falsely positive reports. These two sources of error are so great that no credence can be placed in a laboratory diagnosis of leptospirosis based solely upon darkground microscopic examination of body fluids.

Inoculation of laboratory animals with body fluids has been extensively employed in the past. Following inoculation, animals are observed for febrile responses and development of jaundice, as well as for death with characteristic autopsy findings. The most severe limitation of this method is the extreme range in virulence for laboratory animals encountered in different serotypes of leptospires and even in strains of the same serotype. Hearts' blood cultures from the animal made during the period of leptospiremia following inoculation are frequently successful in demonstration of leptospires which do not produce disease in the animal. This method of animal inoculation followed by culture is, because of its cumbrousness and delay, limited in usefulness to the exam-

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ination of specimens contaminated with other organisms which overgrow leptospires, thus preventing successful direct cultural isolations. A further deterrent to the employment of animals in isolation attempts is the possibility of inapparent leptospiral infection in the laboratory animal resulting in erroneously positive findings. Certain strains of laboratory white mice have been shown to harbor L. ballum and thus make suspect purported isolations from man via this animal.[2]

Aspiration and darkground microscopic examination of peritoneal fluid of laboratory animals for the first four days post-inoculation is, in the experience of European investigators, an often successful method of demonstration of leptospires in body fluids.[3] Negative results, however, have been obtained with specimens found by other techniques to contain leptospires. The rapidity of the method warrants its further consideration.

In our experience, when specimens free of extraneous bacterial contaminants are available, direct cultural examination is the method of choice. Not only is the period of examination shortened, but also a greater proportion of successful isolation attempts is achieved than through the employment of laboratory animals as intermediates. Cultures must be incubated for not less than twenty-eight days before they may be safely discarded as negative. Leptospires are rarely detectable before the seventh day, and in approximately one half the cultures are first detectable on the fourteenth day of incubation.

The most widely employed serological methods for diagnosis of leptospirosis have been the agglutination and the agglutination-lysis tests. These tests have two major limitations. First, if antibodies are to be detected, regardless of the serotype of the infecting leptospira it is essential that a battery of leptospiral serotypes be employed as antigens.[4] In our experience, it is necessary to use a minimum of sixteen serotypes in order to assure adequacy of the antigenic spectrum of the test battery. Second, the coreactions observed between serotypes are such that it is impossible to identify the infecting leptospiral serotype on the basis of highest titers observed. The icterohemorrhagiae A serotype infection in man is notorious in that higher titers against L. canicola than against L. icterohemorrhagiae are frequently encountered.[5] Thus, many purported cases of canicola fever have been found on more critical investigation to be Weil's disease.

The employment of sonic-vibrated antigens in the complement-fixation test for the diagnosis of human leptospirosis has, in our experience, been equally reliable and genus specific as the agglutination-lysis test.[6] Because of the broader complement-fixing antigenic spectrums of these antigens, employment of three serotypes assures an adequate test battery. No information is elicited as to the nature of the infecting strain. The appearance of complement-fixing antibodies somewhat earlier than agglutinating antibodies may be of value to the clinician.

In view of the above considerations, it appears that the problem of laboratory diagnosis might best be approached through joint efforts of local laboratories and central leptospiral reference laboratories. The following procedures are suggested: At the local level, every effort should be made to attempt direct cultural isolation of leptospires, both at the bedside and in the laboratory. Positive cultures should be immediately forwarded to a leptospiral typing center for definitive identification. Serial serum specimens should be examined by complement-fixation and serums giving positive fixation forwarded to a reference laboratory for confirmation by other serologic techniques. This procedure will afford the maximum information within the capabilities of the laboratory services at both levels, and make possible more timely reports to the clinicians requesting laboratory support.

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*Epidemiology of the Leptospiroses**

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The leptospiroses are primarily zoonoses, diseases communicable from animal to animal and from animal to man. Transmission from man to man is so infrequent as to be of no practical significance. Pathogenic leptospires are perpetuated in animal carriers from foci in the tubules of the kidney. Water, food, moist soil, and areas adjacent to animal and human habitations are contaminated by the urine of the leptospiral carriers. The degree of contamination is dependent upon the prevalence and numerical density of the animal carrier populations and their ecology. Although pathogenic leptospires are unable to perpetuate themselves indefinitely outside an animal host they may exist in moderately alkaline water or soil for several weeks.[1] Rodents, small carnivores and certain of the domestic animals are known reservoirs of infection. Each leptospiral serotype has a primary mammalian host species. A single animal species, however, may be the primary host of a number of serotypes of leptospires and may indeed be simultaneously infected with and shed two or more leptospiral serotypes.[2] In addition, the primary host of a single serotype may be one animal species in a given geographical area and another species in a different geographical area. Arthropods have been experimentally demonstrated to be capable of transmitting leptospires from one animal host to another.[3] No naturally occurring arthropod transmission has yet been established. Infection of man results from direct or indirect contact with the contaminated urine of an animal carrier. Infections may occur through the mucous membranes or through minute cuts and abrasions of the skin. Penetration of intact skin has not been conclusively proved. The acidity of the stomach is sufficient to destroy ingested leptospires. However, infection may take place through penetration of the buccal, pharyngeal and esophageal membranes.

Leptospires are found in milk during the acute systemic phase of the disease in lactating animals.[4] They will survive in fluid raw milk for a number of hours and in diluted milk for a period of days.[5] Leptospires are readily destroyed by ordinary pasteurization temperatures. No proved cases of milk-borne leptospirosis of man have been reported in the presently available world literature.

The establishment of renal carriers in the several animal species appears in general related to their position on the phylogenetic scale.[3] Rodents and the small carnivores and marsupials appear to be almost commensurately related to leptospires in that virtually no disease is produced following infection and a lifelong renal carrier state is established. The domestic animals, on the other hand, are less well adapted to the organisms. Clinical disease is frequently encountered and the renal carrier state when established is usually of limited duration. For example, the duration of leptospiruria in cattle and horses appears to be in the order of four months. Man is only infrequently a leptospiral carrier and in these rare instances leptospiruria appears of very limited duration.

The leptospiroses of man may affect both sexes and all ages and occur in all seasons of the year. Most reports, however, describe disease occurring in young males during the warm, wet season. Leptospirosis is an occupational hazard to agricultural laborers, animal husbandrymen, veterinarians, sewer workers, refuse handlers, abattoir employees, and others exposed to rodent infested environments. In addition, large outbreaks may occur regardless of age or sex following swimming in contaminated waters.

Nine serotypes of leptospires are known to exist in North America.[6] The available

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knowledge of their epidemiology is summarized in the following paragraphs:

L. icterohemorrhagiae is harbored primarily in rats, although mice, dogs and mongooses are significant reservoirs. Man may be infected by either direct or indirect contact with the urine of these animals, as in the case of the fishpacking plant employees working in a rodent infested area or the dog owner contracting infection from his pet.

Dogs are the primary reserve of L. canicola although swine and cattle have recently been found to be infected with this organism. The reported human infections have been limited to kennelmen, veterinarians and dog owners with the exception of one water-borne outbreak of approximately two dozen cases following swimming in a contaminated stream.[7]

L. pomona is harbored in swine, cattle, and horses in the United States and transmission of infection to man has followed direct contact with the urine of these animals as well as direct water-borne infection following swimming.[8]

Rats, mice and mongooses are the principal reservoirs of infection with a member of the L. batavia group. Only a single human infection in the United States has thus far been reported and the hosts in this country are not established.[9]

L. autumnalis, the etiologic agent of Fort Bragg fever has been recovered only from man in the United States.[10] No epidemiological investigations have been conducted since its identification as a leptospire. The hosts and manner of infection of man are not established.

House mice, laboratory Swiss mice and wild-caught rats have been found to be infected with L. ballum in the United States but thus far no human infections from this area have been reported. Two naturally acquired human infections have been found in Puerto Rico but the means of infection were not determined.[2]

A member of the grippotyphosa group has been isolated from man in Puerto Rico[2] and serologically demonstrated to infect man in the United States.[11] No animal reservoirs have yet been found.

A new serotype, alexi, of the pyrogenes group has been encountered in Puerto Rico in man and in rats which are the presumptive primary hosts.[2] This serotype has not yet been encountered in the United States.

Two serotypes of the hebdomadis group have been encountered in North America: one, a single infection of man in Puerto Rico for which the primary host is unknown,[2] and the other a widely prevalent infection of cattle in the United States.[12] No human infection with this serotype in the United States has yet been reported but its potential significance as a human pathogen cannot be discounted.

In investigations of the epidemiology of the leptospiroses in North America consideration should be taken not only of the identity of the infecting serotype and its probable primary host, but also of the possibility that future investigations may add to the list of known carriers of these organisms and thus complicate determination of the manner of human infection.

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NEW YORK PATHOLOGICAL SOCIETY

Abstracts of Papers

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The Nature of Acquired Resistance to Grafting with Homologous Tissue

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Rats in which homologous tumor transplants had regressed or those which were immunized with viable, homologous tissues proved to have acquired resistance to grafting with homologous neoplastic or normal tissues. This immunity against homologous tissue was associated with measurable immune activity of viable lymphoid cells. In rats in which tumor transplants had regressed (i.e., presumably more intensely immunized animals) measurable immune activity was also demonstrable in the serum. The properties of these "homologous immune sera" have been studied and have been compared to those of "heterologous immune sera" of rabbits intensely immunized with rat lymphosarcoma. In the stock of rats employed (Sprague-Dawley) no difference in blood groups could be detected and active homologous immune sera neither caused nor inhibited agglutination of rat erythrocytes.

In vitro, the homologous immune serum reacted in no measurable way with viable lymphosarcoma or any other viable rat cells. Even after prolonged incubation of lymphosarcoma cells with homologous immune sera the cells, when separated from the serum and injected into susceptible rats, proved viable and the sera exhibited no detectable loss of immune activity. The heterologous serum following thorough adsorption with rat RBC agglutinated rat lymphosarcoma cells as well as normal rat lymphoid cells gave precipitins with extracts of these cells. Homologous—but not heterologous—serum conferred passive immunity to susceptible rats. Viable—but not injured—lymphoid cells of immune rats when mixed with lymphosarcoma cells inhibited the growth of the latter in susceptible rats. This effect was observed with lymphoid cells from the thymus as well as with those from other sources. Both viable and injured lymphoid cells from spleen or lymph node, but not from thymus, of immunized rabbits were cytotoxic to rat lymphosarcoma cells. Homologous immune sera, unlike heterologous immune sera and unlike the "homologous" immune sera of one highly inbred strain of mouse against tumors of another strain (Gorer) could not be adsorbed with rat erythrocytes nor with viable normal lymphoid or lymphosarcoma cells, but lost their activity when they were exposed to saline extracts from a variety of animal tissues, including those of autologous origin. Thus, whatever the nature of the reaction between the homologous immune serum and the moiety which causes the loss of its activity may be, it does not take place across the uninjured structures of the cell. Contrasting in this "immune system" the relatively high specificity of the antigen (viable, homologous tissue) to the seemingly non-specific reactivity of the immune serum with extracts of autologous, homologous or heterologous tissue, a possible working hypothesis suggests itself: It is conceivable that the anti-

genic moiety which gives rise to immunity against homologous tissue is present in most viable cells and represents a complex which in its entirety is specific for each individual of a given species. This complex is labile and is denatured following injury to the cell, but a haptenic component of the antigen which is alike for all species persists. This hapten is still able to react with the homologous immune serum but is not antigenic.

DISCUSSION

JOHN G. KIDD: Dr. Stoerk has brought new material and new findings and some new concepts to the study of immunity and resistance to transplanted cancer cells. About these I shall speak briefly in a moment. Before doing so, I wish to go back some fifty years to the uncovering of the phenomenon with which Dr. Stoerk is concerned, namely, that of resistance and immunity to transplanted cancer cells. Soon after the work of Hanau, and Moran, and Jensen, and Loeb had made it plain that one can transplant tumor cells from one animal to another, Gaylord and Clowes showed that in some animals implanted tumors failed to grow progressively, while in others they grew briefly and then regressed, the hosts thereafter being immune to reimplantation. Following this demonstration many workers became interested in the phenomenon, and quite a number of facts were learned. Notably, it became apparent initially that this is an artificial phenomenon, concerned only with resistance and immunity to transplanted cancer cells; as Dr. Stoerk has said, one sees nothing comparable with it in the relation of an animal to his own tumor cells. Furthermore, the immunity against tumor cells can be engendered by the prior injection of living normal tissue cells and further studies made it plain that the same laws govern the resistance to transplanted cancer cells and to transplanted normal tissue cells; thus this is an anti-tissue immunity, not an anti-tumor immunity. Finally it soon became obvious to the very early workers that genetic factors play a large part in the phenomenon. Some strains of animals proved notably resistant and others notably susceptible to a given transplantable tumor. When inbred strains of mice became available it was found that a tumor from one individual of a given inbred strain almost always grew when transplanted to other hosts of the same strain, whereas if the growth were put into animals of an alien strain, even of the same breed, the tumors usually regressed; also that in order to engender immunity artificially beforehand one had to use tissues of an alien strain of animals.

Very much has since been learned about the phenomena under investigation here, but actually a large hiatus remains in our knowledge. For the mechanism of the resistance has thus far eluded everyone. No one can say with any real assurance just how the resistant host overcomes the transplanted cell which is put into its tissues—whether this is brought about by cellular factors, by the lymphoid cells or other host cells, for example, or by antibodies, though there has been a great deal of work on the subject. There are several workers whose findings have led them to believe that cellular factors are important. Murphy's name immediately comes to mind in this relation: observing accumulations of lymphocytes around transplanted tissues that were regressing, he went on later to attempt to destroy the lymphocytes by means of radiation, and also to deposit tumor cells in situations—for example, the brains of developing chick embryos—where lymphocytes could not get at them; in these and other ways Murphy accumulated an impressive body of evidence indicating that lymphocytes are the prime agents involved in the phenomenon of resistance to transplanted cancer tissues. Later, as Dr. Stoerk said, Dr. Toolan and I approached the problem from quite another angle and came to substantially the same conclusion. In our material we felt that the lymphoid cells were the only factors that we could discern which overcame transplanted cancer cells in several strains of inbred mice. On the other side there are also several workers with an impressive array of facts indicating that humoral antibodies are responsible for resistance and immunity to transplanted cancer cells. Notable amongst these are Lumsden and Gorer who, working with tumors in rats and mice, have

convinced themselves that humoral factors bring about the destruction of tumor cells in the resistant host.

Now comes Dr. Stoerk with what the artillery people might term a "straddle"; he works both sides of the street; he has both humoral factors and cellular ones. As is inevitable when a man undertakes the study of a phenomenon as old and as much worked over as this one is, Dr. Stoerk has found a number of things that others had previously found. But it is the new aspects of his work which I think I should now speak about. To begin with, he has utilized riboflavin deficiency to bring about the initial regression of lymphosarcomas in his experimental animals, a wholly novel observation. He has also found that there were no blood group differences in the Sprague-Dawley rat which he employed, in this respect his findings being different from those of Lumsden, who, using Wistar rats, found an isoantibody which he correlated with resistance to the Jensen sarcoma. Dr. Toolan, Dr. Ellis and I take a great deal of pleasure in Dr. Stoerk's findings because he has confirmed one of our main observations, namely that if one takes the lymphoid tissues of an animal which is resistant or immune to a given line of tumor cells, and mixes the lymphocytes and tumor cells together in a test tube, the tumor cells do not grow when the mixture is subsequently implanted into susceptible hosts. But as I have indicated, Dr. Stoerk has also found a humoral factor, associated with the gamma globulin fraction of the serum, by means of which he can transfer the immunity passively in the same species. I do not know of any such result in all the experiments that have been made in immunity to transplanted cancer cells thus far. Furthermore, he has made the important observation that the humoral factor, while inhibiting the growth of tumor cells into another situation in a susceptible host given the antibody passively, was not in a strict sense cytotoxic for the cells. For when the two were admixed and later the cells were spun down and thus separated from the immune serum, the cells proved quite viable. The absence of any relation of this humoral factor to blood group agglutinins puts it in a very different category from the humoral factors previously studied by Lumsden and Gorer. Altogether new also is Dr. Stoerk's observation that he could not adsorb the humoral factor by means of viable cells, but could do so by means of cell extracts, whether procured from normal or from neoplastic tissues. Although inclined to the view that this humoral factor is probably an iso-antibody, I am intrigued by it as a novel humoral factor, and one which deserves all the scrutiny that Dr. Stoerk has given it. Perhaps most novel of all is Dr. Stoerk's concept that a labile antigen is present in the intact cell which is somehow destroyed when the cell is injured, leaving, however, a stable hapten which is capable of adsorbing antibody. This too deserves all the scrutiny which Dr. Stoerk can give it, and perhaps some from the rest of us as well.

MARY A. MARCUS: In 1927 I first inoculated a monkey that was given by Dr. William H. Park with injured carcinogenic cells and no local lesion developed, but antibodies of a very low titer did develop. Recently I came to the same conclusion. Later I tried to be very cautious isolating some cells and viruses from a tumor and inoculated a monkey again, and I observed papillomatous growth, but unfortunately the monkey contracted a "cold." I re-inoculated it and it died. Death may have been due to metastasis. Since then I have been working with rabbits and have found that this factor, necrophilic carcinogenic virus (NCV) caused immunization in rabbits, and if I am given a chance to demonstrate my findings I shall be glad to do so.

*Genito-Urinary Tract Lesions in Hodgkin's Disease**

GEORGE T. HOFFMAN, ANTONIO ROTTINO and FREDERICK SUMMERILL

Hodgkin's Disease Research Laboratory, St. Vincent's Hospital

The voluminous literature on Hodgkin's disease contains 33 case reports of genito-urinary tract involvement in this disease.

These reports probably constitute only a small percentage of the total number of cases observed since the disease was first described. In their monograph Jackson and Parker[1] list nineteen cases with renal, ureteral or urinary bladder lesions and combinations thereof in ninety-eight autopsies, but they give no details as to the type of pathologic process observed.

In a series of seventy autopsies performed by us in the past seven years we have observed lesions of Hodgkin's disease in organs of the genito-urinary tract in the following instances:

Organ Involved	*Number of Cases*
Ureter	5
Kidney	9
Urinary bladder	1
Testis	1
Prostate	1
Ovary	1

In addition, there were two other types of lesions of the urinary tract that were considered to be indirectly due to Hodgkin's disease. These were pyelonephritis secondary to the cord-bladder syndrome and renal amyloidosis. Cord-bladders were seen in two patients who had compression of the spinal cord due to proliferation of Hodgkin's tissue in the extradural space. Secondary amyloidosis of the kidneys and other organs was present in seven cases. This 10 per cent incidence of amyloid disease in association with Hodgkin's disease is similar to that found by others.[2]

This report deals briefly with the pathologic aspects and relative clinical significance of the lesions of the urinary tract seen in Hodgkin's disease.

Ureteral Lesions: Ureteral obstruction may be caused by external compression from enlarged lateral aortic or ureteral lymph nodes or by intrinsic involvement of the wall of the ureter. Infiltration of the wall of the ureter by Hodgkin's tissue was seen in five cases. The affected ureter is markedly thickened by white, fibrous tissue, producing a thick cord with a stenotic lumen. If the involvement is irregular the mucosal surface of the ureter may be raised by the proliferating nodules in the submucosa and muscularis. The lesion may be unilateral or bilateral and any portion of the ureter may be affected. The involved ureter may or may not be surrounded by a lymph node mass, and even when it does course through such a mass, it is often possible to separate it by blunt dissection along a definite cleavage plane.

It is apparent that the process may occur through involvement of the intrinsic lymphatics of the wall of the ureter as well as by direct spread from coalescent lateral aortic and ureteral lymph nodes.

Stenosis results in dilatation of the portion of the ureter proximal to the lesion with varying degrees of hydronephrosis and pyelonephritis.

Renal Lesions. Lesions of Hodgkin's disease were found in one or both kidneys in nine cases. Three patterns of involvement were noted. The most common type consisted of single or multiple cortical nodules of varying size which appeared as raised white or grey masses on the surface beneath the capsule. Such lesions were seen in five cases. Less commonly there was spread from ureteral lesions into the pelvis and peri-pelvic fat. In the third type the peri-pelvic tissues were involved by spread from nodes around the renal artery. In one instance of this type the capsule of the kidney

* Presented at the meeting of the New York Pathological Society, October 30, 1952, at The New York Academy of Medicine.

Supported by grants from American Cancer Society and Damon Runyon Fund.

was also involved so that the kidney was completely encased in a thick sac with extension of the process into the renal parenchyma both from capsule and peri-pelvic tissues.

Histologically the renal lesions showed the same pattern as the lymph nodes and other involved organs. In the cortical lesions tubules were destroyed and replaced by granulomatous or sarcomatous tissue with varying numbers of lymphocytes, reticulum cells and Sternberg-Reed cells. Glomeruli were more resistant and were isolated by the surrounding Hodgkin's tissue. Frequently the glomeruli showed thickening of Bowman's capsule and varying degrees of sclerosis of the capillary tufts, but these changes were only seen in those glomeruli that were within the nodule of Hodgkin's tissue.

Lesions in the peri-pelvic tissues simply showed replacement of the fat and adjacent renal parenchyma by tissue with the typical histologic pattern of Hodgkin's disease.

Amyloid Disease of the Kidneys: The renal lesions of amyloid disease noted in this series were typical of secondary amyloidosis with involvement of glomeruli and medullary tubules and did not differ from those seen in amyloidosis secondary to tuberculosis and osteomyelitis.

Other Organs of the Genito-Urinary System: The single lesions of the urinary bladder, testis, prostate and ovary were small. All were of the granulomatous type except that in the bladder, which showed a sarcomatous pattern.

Relative Significance of Lesions of the Genito-Urinary Tract: Generally speaking, the lesions encountered in the urinary tract in this series were of minor significance compared to the massive involvement of other vital organs. In every case Hodgkin's disease was generalized, so that there was no instance of "primary" or pure genito-urinary Hodgkin's disease.

Renal lesions were considered to be the direct cause of death in only one patient. That man, whose total period of illness was only four months, had suppurative pyelonephritis as a result of bilateral ureteral stenosis. All the other patients with ureteral or renal lesions had such massive involvement of the lungs, the liver or both, that the genito-urinary lesions appeared minor in comparison. Renal amyloidosis was always associated with marked amyloid disease of the liver and adrenals and the latter lesions overshadowed those in the kidneys.

Summary

In a series of seventy autopsies on persons with Hodgkin's disease there were eighteen instances of involvement of organs of the genito-urinary system by Hodgkin's disease. In addition there were seven instances of renal amyloidosis.

Hodgkin's disease of the kidney was seen in nine cases. There were single instances of involvement of the urinary bladder, testis, prostate and ovary.

In every case Hodgkin's disease was generalized and the genito-urinary lesions were of minor significance when compared with the massive lesions in other vital organs.

References

1. Jackson, H. and Parker, F. *Hodgkin's disease and allied disorders.* New York, Oxford University Press, 1947.
2. Sternberg, C. Lymphogranulomatose and Reticuloendotheliose. *Ergebn. allg. Path. path. Anat. 30*:1-76, 1936.

Discussion

MEYER M. MELICOW: I would like to add our experience in Hodgkin's disease involving the urinary tract. We have seen six cases. They were part of a study which was made on retroperitoneal tumors. When retroperitoneal Hodgkin's disease involved the urinary tract it was pretty late in the course of the disease. Four patients came to operation, usually exploratory, and all came to autopsy. The youngest patient was thirty-four, the eldest sixty-five years of age. The primary locations in the retroperitoneum were behind the pancreas, below the liver, one case; behind the rectum in the hollow of the sacrum, one case; and along the flanks, four cases. The lesions were very extensive. In the early stages the patients had vague symptoms and wandered from one doctor to another, and from clinic to clinic before a correct diagnosis was made. In one case, the patient was sixty-five years of age and had been studied for a long time because of dull pain in his flank which

caused discomfort. The pyelogram was normal, but the ureter was displaced; such displacement or distortion of the ureter is usually an indication of some trouble in the retroperitoneum. The patient was thought to have a peri-renal abscess for which condition an operation was performed; but biopsy revealed Hodgkin's disease. In another case roentgenological examination showed a shadow of a huge retroperitoneal mass that displaced the ureter, invaded the kidney, and pulled apart the calyces, producing a bizarre pattern; the kidney was secondarily involved by the cancer. In a third case a large retroperitoneal mass displaced the kidney and ureter for a long time but, even in an advanced stage did not cause any change in the calyceal pattern. When the ureter is compressed or invaded, its lumen becomes narrowed and hydronephrosis results.

Some of the symptoms caused by a retroperitoneal tumor such as Hodgkin's disease in these cases include: dull to severe pain in the flank or abdomen, constipation or diarrhea, bloody stools, pain in legs, loss of appetite and weight, fever, ascites, etc. In all patients a vague to definite deep abdominal mass, usually single and lobulated, was palpable. In the group reviewed by us there were thirty-four cases of retroperitoneal lymphosarcomas and six of Hodgkin's disease. The usual complaint in the early stages was backache. In the more advanced stages the patients complained of radicular pain, or higher up of a pleuritic pain. Later came nausea and vomiting. When there was compression of the vena cava the patients usually had edema of the extremities.

Our conclusion after reviewing these cases was that the patients wander about for a long time without correct diagnosis or adequate treatment and that the surgeon or clinician usually does not, but should, think of the possibility of a retroperitoneal tumor causing the vague symptoms.

PAUL KLEMPERER: In the observation of a peri-nephric involvement among these cases, was hypertension present? We had one case, published years ago, of a lymphosarcoma with exactly the same involvement of the kidney in a boy ten years of age. This young patient had been seen when his blood pressure was normal, and he was later re-admitted with extensive retroperitoneal involvement and showed a blood pressure of 160/100.

J. M. RAVID: Was there a sarcomatous pattern in any of your cases of Hodgkin's disease? Also how many cases showed eosinophils?

ANTONIO ROTTINO: The blood pressure in the patient to whom Dr. Klemperer referred was low—84/60. Blood pressures taken before the final admission to the hospital were never elevated. At autopsy no hypertrophy of the heart was observed. In other words, we have no evidence that the peri-renal capsular involvement resulted in hypertension.

In reply to Dr. Ravid's question, one of the cases exhibited Hodgkin's sarcoma. In the remaining cases, the lesions were characterized by marked fibrosis, diminution of lymphocytes and reticulum cells. Eosinophils were not conspicuous.

TWENTY-SIXTH GRADUATE FORTNIGHT

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DISORDERS OF THE BLOOD AND THE BLOOD-FORMING ORGANS

OCTOBER 19-30, 1953

EVENING LECTURE PROGRAM

MONDAY, OCTOBER 19

PRESIDENTIAL ADDRESS
ALEXANDER T. MARTIN

ERYTHROPOIESIS: NORMAL AND ABNORMAL
Ludwig Kast Lecture
WILLIAM B. CASTLE, Professor of Medicine, Harvard Medical School

IRON METABOLISM
S. GRANICK, Ph.D., Associate Member of the Rockefeller Institute

TUESDAY, OCTOBER 20

PRINCIPLES IN THE MANAGEMENT OF ANEMIAS
Carpenter Lecture
MAXWELL M. WINTROBE, Professor of Medicine, University of Utah College of Medicine

HEMOGLOBIN AND BILE PIGMENT METABOLISM
IRVING M. LONDON, Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University

WEDNESDAY, OCTOBER 21

THE HEMOLYTIC STATES
WILLIAM H. CROSBY, Lt. Col., MC, USA, Chief Department of Hematology, Army Medical Service Graduate School, Washington, D. C.

HEREDITARY ANEMIAS
R. JANET WATSON, Associate Professor of Medicine, State University of New York, College of Medicine at New York City

THURSDAY, OCTOBER 22

ANEMIAS IN INFANCY AND CHILDHOOD: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS
CARL H. SMITH, Associate Professor of Clinical Pediatrics, Cornell University Medical College

BASIC MECHANISMS OF THE HEMOSTATIC PROCESS
MARIO STEFANINI, Associate Professor of Medicine, Tufts College Medical School

FRIDAY, OCTOBER 23

HEMOPHILIA
K. M. BRINKHOUS, Professor of Pathology, University of North Carolina School of Medicine

THE THROMBOCYTOPENIC PURPURAS
EUGENE L. LOZNER, Associate Professor of Medicine, State University of New York Upstate Medical Center, Syracuse

MONDAY, OCTOBER 26

WHITE BLOOD CELLS IN HEALTH AND DISEASE
CHARLES A. DOAN, Dean and Director of Medical Research, Ohio State University Health Center, Columbus, Ohio

POLYCYTHEMIA VERA: ITS COURSE AND TREATMENT
LOUIS R. WASSERMAN, Hematologist, The Mount Sinai Hospital, New York

TUESDAY, OCTOBER 27

LYMPHOMAS AND LEUKEMIA
Harlow Brooks Lecture
NATHAN ROSENTHAL, Consulting Hematologist, The Mount Sinai Hospital, New York

THE THERAPY OF LEUKEMIA
JOSEPH H. BURCHENAL, Professor of Medicine, Sloan-Kettering Division of Cornell University Medical College

WEDNESDAY, OCTOBER 28

HYPERSPLENISM
WILLIAM DAMESHEK, Professor of Clinical Medicine, Tufts College Medical School

CURRENT PROBLEMS IN BLOOD TRANSFUSION
PETER VOGEL, Director of the Blood Bank, The Mount Sinai Hospital, New York

THURSDAY, OCTOBER 29

FACTORS MODIFYING THE EFFECT OF RADIATION ON THE BLOOD AND BLOOD-FORMING TISSUE
LEON O. JACOBSON, Professor of Medicine, The University of Chicago

RETICULOENDOTHELIOSIS
PAUL KLEMPERER, Pathologist, The Mount Sinai Hospital, New York

FRIDAY, OCTOBER 30

CLINICAL IMPLICATIONS OF PLASMA FRACTIONATION
I. HERBERT SCHEINBERG, Instructor in Medicine, Harvard Medical School

BLOOD VOLUME IN HEALTH AND DISEASE
SOLOMON A. BERSON, Assistant Director, Radioisotope Unit, Veterans Administration Hospital, Bronx, N. Y.

MORNING PANEL PROGRAM

11:00 A.M. at the Academy

Monday, October 19

NUTRITIONAL ANEMIAS.....*Chairman:* JOSEPH C. TURNER

Wednesday, October 21

METHODS IN HEMATOLOGY.....*Chairman:* DANIEL STATS

Friday, October 23

ERYTHROBLASTOSIS FETALIS.....*Chairman:* AARON KELLNER

Monday, October 26

THE ACTION OF DRUGS AND TOXIC AGENTS ON THE BLOOD PICTURE.....*Chairman:* PAUL REZNIKOFF

Wednesday, October 28

THERAPY OF LEUKEMIA.....*Chairman:* LLOYD F. CRAVER

Friday, October 30

THE PROBLEMS OF TRANSFUSIONS.....*Chairman:* PETER VOGEL

HOSPITAL CLINICS PROGRAM

CALENDAR OF CLINICS

All Clinics will be held from 2 to 5 P.M.

First Week

(AT THE HOSPITALS)

Monday, October 19

1. Memorial
   Hospital Representative: LLOYD F. CRAVER
2. Flower-Fifth Avenue
   Hospital Representative: LINN J. BOYD

Tuesday, October 20

3. Polyclinic
   Hospital Representative: JAMES P. CROCE
4. Lenox Hill
   Hospital Representative: CARL REICH

Wednesday, October 21

5. St. Vincent's
   Hospital Representative: ANTONIO ROTTINO
6. Veterans Administration, Bronx
   Hospital Representative: JOSEPH GENNIS

Thursday, October 22

7. Roosevelt
   Hospital Representative: R. STERLING MUELLER
8. St. Luke's
   Hospital Representative: LUIS A. AMILL

Friday, October 23

9. Morrisania
   Hospital Representative: HERMAN L. FROSCH
10. Joint Diseases
    Hospital Representative: CARL REICH

Second Week

(AT THE ACADEMY)

Monday, October 26

11. University
    Hospital Representative: EDWARD H. REISNER, JR.
12. Bellevue
    Hospital Representative: CHESTER H. WHITNEY

Tuesday, October 27

13. Beth Israel
    Hospital Representative: LEON SUSSMAN
14. Presbyterian
    Hospital Representative: JOSEPH C. TURNER

Wednesday, October 28	15.	St. Clare's *Hospital Representative:* CARL REICH
	16.	New York *Hospital Representative:* RALPH L. ENGLE, JR.
Thursday, October 29	17.	Harlem *Hospital Representative:* NATHAN ROSENTHAL
	18.	Mt. Sinai *Hospital Representative:* LOUIS WASSERMAN
Friday, October 30	19.	Kings County, University Division *Hospital Representative:* R. JANET WATSON
	20.	Montefiore *Hospital Representative:* SAMUEL MELAMED

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

1953 — 1954

Fridays at the Academy — 4:30 P.M.

NOVEMBER 6, 1953 — **CURRENT CONCEPTS IN THE MANAGEMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS**
Moderator: LAWRENCE S. KUBIE

DECEMBER 4, 1953 — **CURRENT CONCEPTS IN THE MANAGEMENT OF ASTHMA, EMPHYSEMA AND CHRONIC PULMONARY INFECTIONS**
Moderator: DICKINSON W. RICHARDS, JR.

JANUARY 8, 1954 — **CURRENT CONCEPTS IN THE MANAGEMENT OF THE MENOPAUSE, FEMALE AND MALE**
Moderator: HOWARD C. TAYLOR, JR.

FEBRUARY 5, 1954 — **CURRENT CONCEPTS IN THE MANAGEMENT OF ARTERIOSCLEROSIS**
Moderator: DAVID P. BARR

MARCH 5, 1954 — **CURRENT CONCEPTS IN THE MANAGEMENT OF ELECTROLYTE DISTURBANCES**
Moderator: E. HUGH LUCKEY

APRIL 2, 1954 — **CURRENT CONCEPTS IN THE USE OF ANTIBIOTICS**
Moderator: YALE KNEELAND, JR.

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MEDICAL RESEARCH FORUM

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THE NEW YORK ACADEMY OF MEDICINE will reinstitute the Forum for Clinical Research during the coming academic year 1953-1954. By accepting only a limited number of presentations of new, original and interesting work, the Committee plans to improve the quality of this Forum over that of the Clinical Research meetings of former years. Investigators may present results of original research in clinical medicine at this Forum, to be held Thursday, January 28, 1954, at 8:00 P. M.

This Forum is being arranged by the Committee on Medical Education of the Academy with the following stipulations:—

1. Presentations will be confined to *recent* original research in clinical medicine, surgery, or to research which is applicable to medicine or surgery in all clinical branches.

2. Presentations should be reports of work done within the last year or of progress in a continuing project. Previous submission to or presentation before a society will not prejudice the opportunity for presentation at the Forum.

3. In submitting application, the investigator is requested to state whether this work has been published, in toto or abstract, or has been submitted for publication; also, in cases where the investigator is working under the head of a department of a hospital or research institute, approval of the head of department is requested.

Presentations will be limited to twelve minutes. A period of free discussion will follow each presentation.

The publication of presentations is not a necessary condition but the Academy plans to publish promptly abstracts of presentations, if the author so desires. In order to expedite publication of abstracts, the Committee requests that the abstract submitted by the investigator be carefully prepared in the form in which publication is desired, with the understanding that publication of the abstract in the *Bulletin* of the Academy shall not preclude publication by the author in any other journal.

The Committee extends an invitation to all research workers of Greater New York to submit *an abstract of proposed presentation in QUADRUPLICATE*, not to exceed five hundred words in length, to the Secretary of the Committee on Medical Education of the Academy *during September and October 1953 and not later than November 1, 1953.* A formal invitation to participate in this program will then be extended by the Committee to the authors of papers selected for presentation.

ROBERT L. CRAIG, M.D., *Executive Secretary*
Committee on Medical Education
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1. Savage, M. B., in discussion of Davis, C. H., and Grand, C. G.: Trichomonas Vaginalis Donné: An Evaluation of Experimental and Clinical Data, Am. J. Obst. & Gynec. *64*: 544 (Sept.) 1952.

2. Upton, J. R.: Symposium: Certain Aspects of Office Treatment in Obstetrics and Gynecology: Trichomonas Vaginalis Vaginitis, West. J. Surg. *60*:222 (May) 1952.

3. Kleegman, S. J.: Treatment of Trichomonas Vaginitis, GP *6*:49 (Aug.) 1952.

4. Kanter, A. E.: The Recognition and Treatment of Vaginal Lesions, Postgrad. Med. *12*:457 (Nov.) 1952.

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1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.

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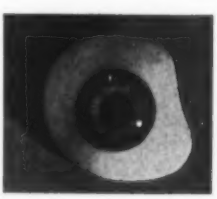

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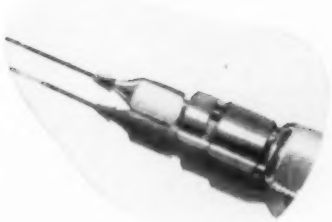

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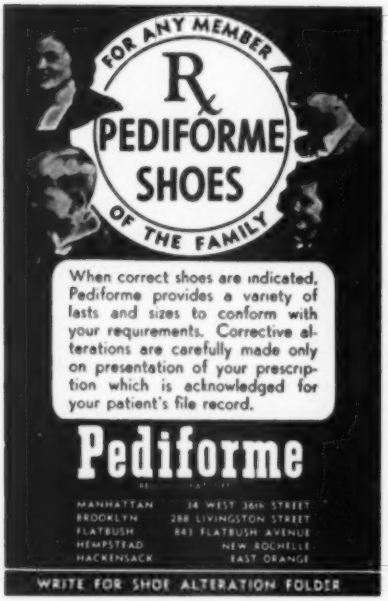
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1. Meller, R. L., and Resch, J. A.: *Bull. Univ. Minnesota Hosp.*, 20:78, Oct. 8, 1948.
2. Meller, R. L., and Resch, J. A.: *Postgrad. Med.*, 6:452, Dec., 1949.

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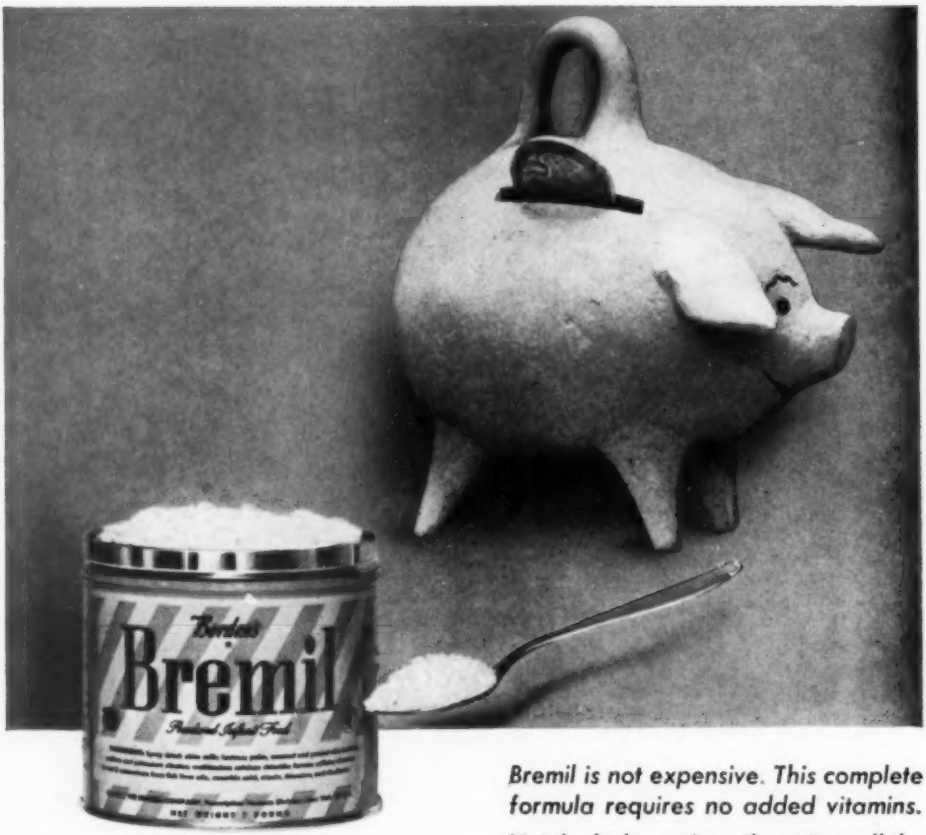

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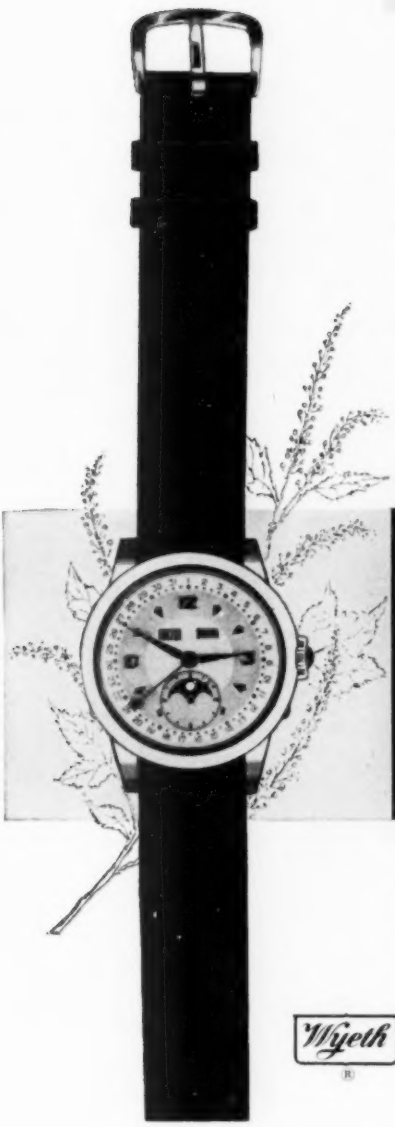

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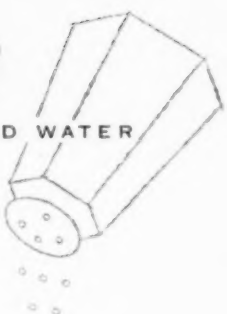

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